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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

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BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 15 1959

INCIDENCE OF HYPERTENSION AFTER PREGNANCY TOXAEMIA

BY

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In spite of an extensive literature, which was reviewed in two previous papers (Gibson, 1954, 1956), there is still some difference of opinion on whether permanent and significant hypertension is a frequent sequel to pregnancy toxaemia in women who enter pregnancy with normal blood pressures; and again about the amount of damage which may be done by a toxaemic pregnancy in a woman already hypertensive. The three major difficulties of assessment are: (1) the difficulty of definition and classification; (2) the fact that few women have had their blood pressures taken before pregnancy started, and it is well known that pressures taken during the second trimester of pregnancy may give unusually low readings; and (3) the fact that, in a normal population, blood pressure varies with age, so that in a follow-up study final blood pressures must be expected to be somewhat higher than initial readings taken some years previously. For all these reasons one of us was about to embark on yet another follow-up study of a small series of cases of pregnancy toxaemia observed a few years ago (Platt, Stewart, and Emery, 1958), but on reading the literature it seemed that the very much larger series of cases observed by Gibson (1954, 1956) (which is referred to in this paper as the Belfast series) was capable of further analysis. This paper is therefore a re-examination, jointly by physician and obstetrician, of the Belfast series.

In this series Gibson took the figure of 140/90 to be the arbitrary dividing line between normal blood pressure and hypertension. If either the systolic or diastolic pressure was below this level the patient was regarded as normotensive. Of 1,420 toxaemic pregnancies in the series, 95% of the women were re-examined an average of four years later. Of these, 63.6% were adjudged, after review, to be cases of pre-eclamptic or eclamptic toxaemia, and 11.7% to be cases of chronic hypertension complicated by pregnancy. 1.9% were classed as chronic renal disease, and 22.8% remained unclassified, this large residue of unclassified cases being due usually to the fact that blood-pressure readings in early pregnancy had not been recorded. Using again the criterion of 140/90, Gibson found that about 30% of patients had hypertension after pre-eclamptic toxaemia. He found that neither the duration of the toxaemia—that is, the length of conservative treatment—nor the severity of the toxaemia had a significant effect on the incidence of hypertension as a sequel; the most important factor was the age at time of review—49% of women aged 40 to 44 years and 65% of women aged 45 to 49 years were hypertensive on this assessment.

Case Material.—The case records have been divided into two groups: (1) the toxaemic series, consisting of 446 cases in which the blood pressure was found to be below 140/90 during or before the 20th week of pregnancy, and which satisfy the diagnostic criteria of toxaemia (Gibson, 1954); and (2) the hypertensive series, in which the blood pressure was found to be 140/90 or more during or before the 20th week of pregnancy.

Toxaemic Series

The main objects of the re-examination were to compare the initial and later blood pressures of these women with those of a general population of women in the same age groups. For our controls we have taken the population of 1,204 unselected females recorded by Hamilton, Pickering, Fraser Roberts, and Sowry (1954a). For the sake of brevity this is referred to as the London series. It must be noted, however, that our toxaemic series is not strictly comparable with a series of unselected women, because we have arbitrarily excluded anyone with a blood pressure of 140/90 or over, and the London series clearly shows that in the older age groups something approaching a third of all women are likely to have blood pressures higher than this. Table I and Fig. 1 show the systolic pressures and Table II and Fig. 2 the diastolic pressures of the toxaemic series in early pregnancy and again some four years after the pregnancy, set out as percentages and compared with the London series. It will be seen at a glance that the distribution of blood pressures of these women in early pregnancy closely corresponds with the distribution we would expect from the London series, except in the later age group (40–49), where, as we would expect, the exclusion of cases with pressures of over 140/90 significantly alters the distribution. Yet the blood pressures four or so years later are all shifted to the right and no longer conform to the expected distribution of blood pressures in a population of corresponding age. This occurs in spite of the fact that, initially, women with pressures over 140/90 were excluded.

It should be noted that this method of setting out the results appears to dispose of two of the difficulties encountered in this kind of study. In the first place, age is accounted for because the women are being

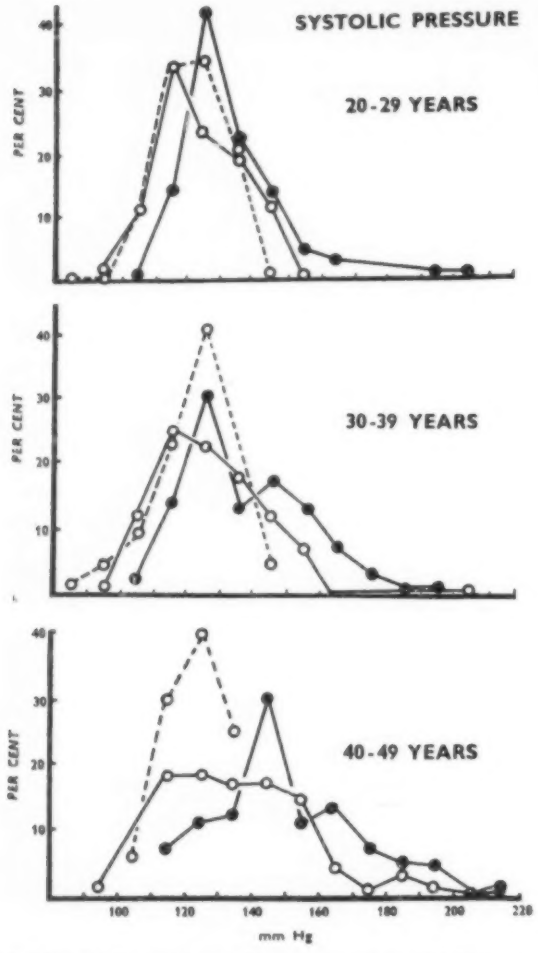

FIG. 1.—Distribution of systolic pressures in women before and after a toxaemic pregnancy compared with an unselected series of women of similar age. O- - - -O = Initial pressure. O——O = London series. ●——● = Follow-up.

compared with a population of their own age group; for instance, a woman who was 27 during her pregnancy will be in the age group 30–39 when her blood pressure four or five years later is recorded. In the second place, the reliability of the blood pressure during early

TABLE II

Age	Total Cases		Diastolic Pressures 40/45	50/55	60/65	70/75	80/85	90/95	100/105	110/115	120/125
Under 20	16	Initial pressure			7	7	2				
	0	Follow-up pressure			0	0	0				
		Initial pressure %			44	44	12·5				
		Follow-up pressure %			0	0	0				
		London series %		4	27	52	18				
20–29	277	Initial pressure	2	6	67	122	70	10	0	0	
	182	Follow-up pressure			7	57	87	26	4		1
		Initial pressure %	1	2	24	44	25	4			
		Follow-up pressure %			4	31	48	14	2		1
		London series %		1	18	49	25	8			
30–39	133	Initial pressure		2	15	62	44	10			
	189	Follow-up pressure			7	44	71	42	22	3	
		Initial pressure %		1·5	11	47	33	7·5			
		Follow-up pressure %			4	23	38	22	12	2	
		London series %		1	16	40	30	10	3	1	0·5
40–49	20	Initial pressure			2	9	8	1			
	74	Follow-up pressure				4	24	20	19	5	2
		Initial pressure %			10	45	40	5			
		Follow-up pressure %				5	32	27	26	7	3
		London series %		0·5	6	29	37	17	5	4	1
50–59	1	Follow-up pressure					1				

TABLE I.—*Systolic Pressures*

Age	Total Cases		80/85	90/95	100/105	110/115	120/125	130/135	140/145	150/155	160/165	170/175	180/185	190/195	200/205	210/215
Under 20	16	Initial pressure			4	3	4	4	1							
	0	Follow-up ,,			0	0	0	0	0							
		Initial ,, %			25	19	25	25	6							
		Follow-up ,, %			0	0	0	0	0							
		London series %		2	13	45	29	11	0							
20–29	277	Initial pressure	1	1	30	91	95	55	4							
	182	Follow-up ,,			2	25	75	40	23	8	5			2	1	1
		Initial ,, %	0·4	0·4	11	33	34	20	1·4							
		Follow-up ,, %			1	14	41	22	13	4	3			1	0·5	0·5
		London series %		2	11	33	23	19	12	0·6						
30–39	133	Initial pressure	1	5	12	30	54	24	7							
	189	Follow-up ,,			4	25	57	24	32	25	13	5	2	2		
		Initial ,, %	1	4	9	23	41	18	5							
		Follow-up ,, %			2	13	30	13	17	13	7	3	1	1		
		London series %		1	12	25	22·5	18	12	7			0·5		0·5	
40–49	20	Initial pressure	0	0	1	6	8	5								
	74	Follow-up ,,			5	8	8	9	23	8	9	6	3	2		1
		Initial ,, %			5	30	40	25								
		Follow-up ,, %				7	11	12	31	11	12	8	4	3		1
		London series %		1	6	18	18	17	17	14	4	1	3	1	0·5	0·5
50–59	1	Follow-up pressure							1							

pregnancy seems to be established, because if unusually low readings were being encountered, giving a falsely low baseline, they would not compare so accurately (in the younger age groups) with the London series. The average duration of pregnancy at which the initial blood pressure was recorded was 15 weeks, and, as a further check, we calculated the average blood pressures in the two main age groups, taking only those cases in which the blood pressure had been recorded at the 13th week or earlier. There were 143 such cases, and in the 20–29 age group their average blood pressure was 119/72, compared with 119/74 in the whole group; and in the 30–39 age group the average was 120/75, compared with 120/76 for the total of that group. There is thus no significant difference in our series between blood pressures taken during the first 13 weeks and during the first 20 weeks.

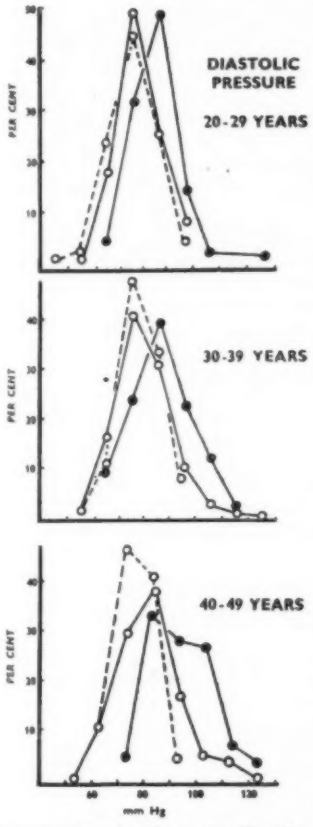

FIG. 2.—Same as Fig. 1, but diastolic pressures. Key as Fig. 1.

From Table III and Fig. 3 it will be seen that the mean initial blood pressure in the 20–29 age group was 119/74, and the follow-up blood pressure 130/81. In the 30–39 age group the initial figure was 120/76 and the follow-up figure 135/84. In the 40–49 age group the initial figure was 121/76 and the follow-up figure 148/93.

We can also examine the data in another way. Table IV shows the actual mean gain in pressure of the toxaemic women compared with the gain in pressure which would be expected in women of the same age after the passage of four to five years (as calculated from the London series). In each case the gain in pressure far exceeds the expected gain. It is greater in the older groups, but this may not indicate a greater risk, because a gain of 10 mm. diastolic pressure in a woman of 20 is probably equivalent to a gain of 15 mm. in a woman of 40 (see later).

TABLE III.—*Mean Blood Pressures*

Age		Systolic	Diastolic
Under 20	Initial	120	63
	Final	(None)	(None)
	London series	116	70
20–29	Initial	119	74
	Final	130	81
	London series	120	75
30–39	Initial	120	76
	Final	135	84
	London series	124	80
40–49	Initial	121	76
	Final	148	93
	London series	134	83

As a result of this examination of the Belfast data there seems to us to be little doubt that, as a statistical finding, pregnancy toxaemia causes an increase in blood pressure which is quite beyond anything which can be explained by the mere passage of time. As to the individual, there are of course a large number of cases in which no significant rise of blood pressure occurs at all, and hypertension of a degree likely to affect seriously the expectation of life is very rare. Only 17 of these 446 women were left with a diastolic pressure of 105 or over, and several of these had initial pressures which were at the upper limit for inclusion in the toxaemic series—for example, pressures of 135/90.

Some of the women had had another pregnancy between the initial (early pregnancy) blood pressure and the follow-up study. In some instances the second pregnancy had also been toxaemic. To save breaking down the material into a number of small groups we have included these, taking no account of the second pregnancy. In most cases there is no obvious difference between those who had one and those who had two pregnancies. One extreme case is that of a girl of 18 whose blood pressure at the 18th week of her second pregnancy was 130/80. This rose to 165/110 during the toxaemia. When seen four years later, after another intervening toxaemic pregnancy, her pressure was 190/115.

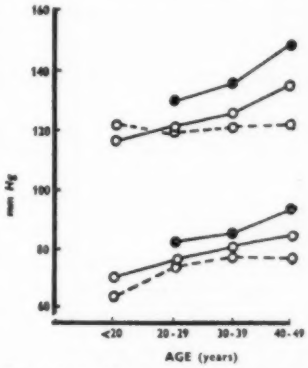

FIG. 3. — Mean blood pressures (systolic and diastolic) of women before and after a toxaemic pregnancy compared with mean blood pressures of an unselected series of women of similar age. Key as Fig. 1.

TABLE IV.—*Actual and Expected Gains in Mean Blood Pressures by an Increase in Age of Four to Five Years*

Initial Age	Actual		Expected	
	Systolic	Diastolic	Systolic	Diastolic
Under 20	10·6	8·8	2·0	2·0
20–29	12·1	9·1	2·5	2·0
30–39	20·5	13·2	4·0	2·5
40–49	31·3	17·3	5·0	3·0

Hypertensive Series

This series of 92 cases (95 cases, with 3 deaths) includes all those women whose initial blood pressure at the 20th week of pregnancy or before was 140/90 or more. The average duration of pregnancy at which the initial blood pressure was taken was again the 15th week: again we made a check to see if unusually low readings were being obtained because of the pregnancy, but we found that the 34 cases in which the initial blood pressure was recorded at the 13th week or before gave an average diastolic pressure only 3 mm. higher than the average for the whole series of 92 cases. This was probably of no significance.

It was of course impossible to compare this selected series of hypertensive women with any normal population, and we therefore converted their blood pressures into scores adjusted for age according to the method of Hamilton, Pickering, Fraser Roberts, and Sowry (1954b). By this method any blood pressure can be converted into a corresponding pressure at the age of 60, so that pressures at all ages can be compared. For instance, at the age of 35 the average diastolic pressure for a woman is 80. If her diastolic pressure is in fact 100, or 20 mm. above the average, she scores, not +20, but +25, because, owing to the curve for age, her blood pressure at 60 will probably be 25 mm. above average. A woman of 20 with a diastolic pressure of 100 would, however, score +55 on the same scale, whereas a woman of 45 with a diastolic pressure of 100 would score only +15. This seemed to us to be the only way of trying to make a comparison between the starting pressures of these hypertensive women and their blood pressures recorded about four years later.

The variations from case to case in this series are enormously greater than those in the toxaemic series. Some women with quite high blood pressures seem to be completely unaffected by the pregnancy—in fact, the follow-up pressure may even be lower than the initial one. In other cases extreme rises of pressure are found; for instance, from 140/90 in a woman of 42, to 220/140 five years later. Until we know more about the factors concerned in the development and progression of hypertension, it is somewhat doubtful whether the comparison made here has much validity, but, for what it is worth, the average score for starting systolic pressure was +51; at the follow-up this had increased by 17. The score for the initial diastolic pressure was +25, and this had increased by 8 at the follow-up examination. Translating this back into real blood pressures—for instance, in a woman aged 40—an initial pressure of about 165/100 would be converted into one of 180/110; as the effect of age is elimated this would seem to be a significant increase attributable entirely to the pregnancy, but again let us remark that fluctuations between individuals are extreme, and there is comparatively little correlation between the height of the starting pressure and the gain of pressure which may be anticipated.

Comment

Although we believe that this paper brings to light some facts about the late prognosis of pregnancy toxaemia which have not been previously shown so clearly, it has to be admitted that the evidence could be challenged on at least two points. The first is that the initial pressure and the follow-up pressure were in most cases not recorded by the same person. If this were a serious source of inaccuracy we do not think the records would show such a clear similarity between the initial pressures and the pressures recorded in the London series for the same age groups; neither do we think that it would show such a regular shift to the right in the follow-up pressures of all age groups. The second point is that we have used as our controls the records of blood pressures from an unselected population—that is, the London series. The ideal control would have been a series of women who had passed through a non-toxaemic pregnancy.

Summary and Conclusions

Further consideration of a previously recorded series of 446 cases of pre-eclamptic toxaemia in women whose blood pressure early in pregnancy was normal clearly shows that their mean blood pressures approximately four years after the toxaemic pregnancy are much higher than the mean pressures which would be expected in an unselected population of women of similar age. Nevertheless, *severe* hypertension is a rare sequel of toxaemic pregnancy in a woman previously normotensive. Similarly, in women who had toxaemic pregnancies superimposed on hypertension the rise of blood pressure on re-examination was more than could be accounted for by an increase of age of approximately four to five years.

We are grateful to Professor C. H. G. Macafee, in whose department the original work of this survey was carried out.

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ISCHAEMIC ELECTROCARDIOGRAMS IN SYMPTOMLESS MEN

WITH A NOTE ON THE SERUM LIPOPROTEINS

BY

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Much reliance is placed on the electrocardiogram (E.C.G.) in the diagnosis of ischaemic heart disease, especially in cases where the pain is atypical. Most physicians would be prepared to disregard a normal tracing in a patient with a classical history of effort pain or with clinical manifestations of myocardial infarction; but when these features are equivocal their interpretation is apt to be influenced by the electrocardiographic findings. While this approach is usually justified, the wording of some requests for electrocardiography ("Chest pain . . . ? evidence of ischaemia") at least conveys the impression that the tracing is to be used as a diagnostic arbiter, on the thesis that chest pain with an abnormal E.C.G. is necessarily cardiac pain. It should, however, be remembered that coronary artery disease is commonly found at necropsy when there have been no referable symptoms during life, apd it is therefore debatable whether electrocardiographic evidence of myocardial ischaemia can invariably be equated with clinical manifestations. Hence, to assess the reliability of the E.C.G. in diagnosis it is important to know how often an ischaemic tracing may be a chance finding.

The literature contains several reports of such tracings being recorded in subjects without chest pain. The significance of many of these series is questionable, either because cases of hypertension or valvular disease (which produce similar electrocardiographic abnormalities) were included, or because insufficient leads were recorded. Using full leads in clinically healthy subjects, Wosika *et al.* (1950) noted ischaemic tracings in 21% of people over 80, and Acheson (1957) noted them in 10% of R.A.F. personnel aged between 19 and 54.

However, the maximum incidence of coronary artery disease is in men in their fifties and sixties (Peel, 1955)—that is, between the age groups covered by the above two series. It is therefore among these that the assessment of chest pain assumes most importance. We have investigated the incidence of ischaemic E.C.G.s in men without chest pain in the age group 50 to 80, adopting rigorous criteria to exclude other causes of electrocardiographic abnormality.

The association between abnormalities in the serum lipoproteins and coronary atheroma (Gofman *et al.*, 1950; Jones *et al.*, 1951) has been the subject of much discussion in recent years (for review, see Oliver and Boyd, 1957); consequently we also studied the serum lipoproteins in these men and compared them with cases of coronary disease.

Method

The subjects studied were 100 male hospital in-patients, aged at least 50, who conformed to the following criteria: (1) no chest pain, or history thereof, or shoulder pain; (2) no evidence of valvular or any other type of heart disease, or heart failure, or pericarditis; (3) diastolic blood pressure not greater than 90 mm. Hg; (4) no cardiac enlargement on *x*-ray film; (5) no renal or endocrine disorder capable of producing major electrolyte disturbance; (6) no diabetes; (7) no syphilis; (8) serum cholesterol under 300 mg./100 ml.; (9) no evidence of peripheral or cerebral vascular disease; (10) no arrhythmia other than ectopic beats. Other causes of electrocardiographic abnormality were excluded by criteria 2 to 5; and conditions with a high incidence of coronary disease were excluded by criteria 6 to 9.

The conditions which had caused admission to hospital are listed in Table I. Fifty-seven of the men were aged 50 to 59, 26 were 60 to 69, and 17 were 70 to 80. Each was questioned and examined clinically by one of us (D. W.) and by at least one other medical officer. A 6-foot (183-cm.) chest film was taken for heart size. A 12-lead E.C.G. (I, II, III, AVR, AVL, AVF, V_{1-6}) was recorded at rest. The subject was then exercised (unless unfit) by running or walking briskly up several flights of steps, stopping at his own request. Thirty patients were not fit for exercise. After exercise, leads V_5 and V_6 were repeated at two-minute intervals for 10 minutes.

TABLE I.—*Diseases in the 100 Cases Investigated*

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Peptic ulcer	30	Disseminated sclerosis	1
Neoplastic lesions	29	Malignant exophthalmos	1
Respiratory infections	8	Trigeminal neuralgia	1
Reticulosis	6	Senile osteoporosis	1
Cirrhosis hepatis	4	Herpes zoster	1
Disk prolapse	3	Cholecystitis	1
Intestinal infections	3	Investigations negative or inconclusive	9
Rheumatoid arthritis	1		
Dermatomyositis	1		

We used the usual criteria for electrocardiographic evidence of myocardial ischaemia: large Q waves, flattening or inversion of T waves, and depression of the ST segment at rest or after exercise. Although such ST and T changes are not specific, and can be produced by ventricular hypertrophy, pericarditis, and electrolyte disturbances, the selection of cases ensured the exclusion of such causes. Flattening of the T waves alone or ST depression of less than 1 mm. was not accepted as evidence of ischaemia unless square depression of the ST segment of greater amplitude followed exercise; if no change occurred the tracings were regarded as equivocal and were not included in the ischaemic total. The changes induced by exercise were assessed when the heart rate had returned to the resting figure.

Since the investigation was begun 35 men have died as a result of the illnesses which occasioned the original admission. Necropsy was performed in 19 who died in hospital, and in 12 of these the coronary arteries were examined radiographically after injection of a suspension of bismuth oxychloride. The technique was similar to that described by Shillingford (1950). The survivors are being seen annually for clinical examination, electrocardiography, and lipoprotein study; so far 29 have been followed for up to three years.

Results

The electrocardiographic findings are shown in Table II. Abnormal tracings were recorded from 12 patients; examples are shown in Figs 1–4. Since none of these men had any serious electrolyte disturbance, pericarditis, or any lesion causing ventricular strain, the ST and T wave abnormalities were interpreted as due to myocardial ischaemia. Three more tracings showed right bundle-branch block: as this may be a

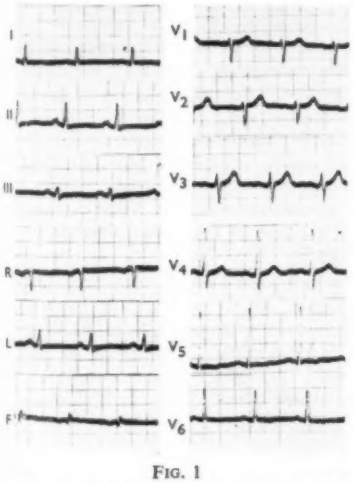

FIG. 1

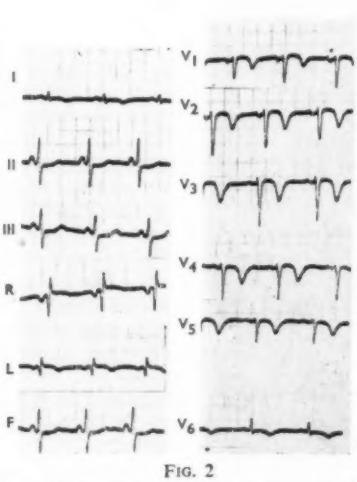

FIG. 2

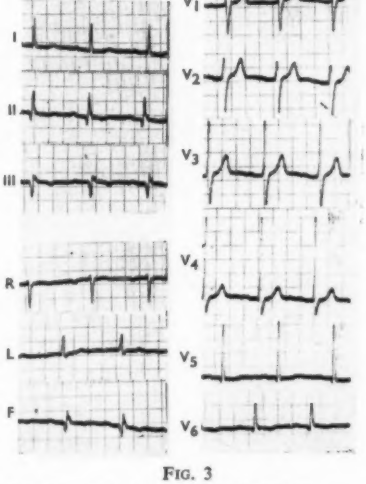

FIG. 3

FIG. 1.—Ischaemic pattern in leads I, II, L, V_5, and V_6. FIG. 2.—Anterior (intramural) infarction. FIG. 3.—Posterior infarction.

congenital abnormality they were excluded from the ischaemic total, as were another three that showed ischaemic changes at low haemoglobin levels but became normal after treatment of the anaemia. Ischaemic tracings were recorded in four men aged 50–59, four aged 60–69, and four aged 70 and over.

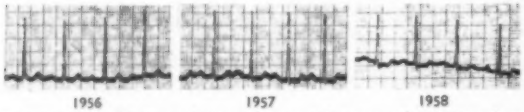

FIG. 4.—Lead V_5 two minutes after exercise test. Annual tracings with change from a normal to an ischaemic pattern. There was no pain on exercise, and the man has remained symptom-free with unimpaired effort tolerance.

TABLE II.—*Electrocardiographic Findings in 100 Men Without Chest Pain or Evidence of Heart Disease*

Ischaemic		12
Infarction	2	
ST segment and T waves abnormal at rest	8	
Normal at rest, ST segment and T waves abnormal after effort	2	
Abnormals not included in ischaemic total		12
Right bundle-branch block	3	
Abnormal during anaemia, normal after treatment	3	
Equivocal	6	
Normal at rest and after effort		76

Of the 19 cases that later came to necropsy, six had had ischaemic E.C.G.s during life. In all 19 the absence of any cardiac lesion, other than coronary atheroma, was confirmed. In 12, including three with ischaemic E.C.G s, the coronary arteries were examined radiographically, after injection of bismuth oxychloride in gelatin. Evidence of significant abnormality, sufficient to cause myocardial ischaemia, was sought, using two criteria: (1) an increase in the number of small anastomotic vessels (Shillingford, 1950); and (2) development of a subendocardial plexus, as described by Fulton (1956).

A normal vascular pattern was demonstrated in six cases (Fig. 5), all with normal E.C.G.s. An increased anastomotic pattern, with a subendocardial plexus

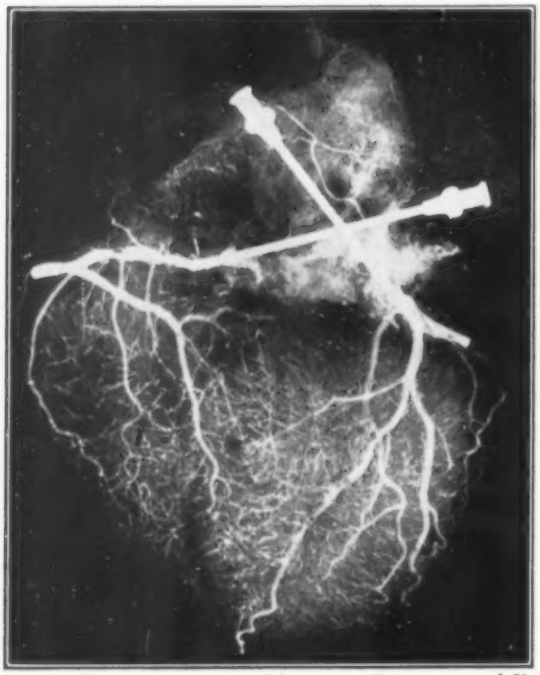

FIG. 5.—Normal coronary arterial pattern. From a man of 73 with a normal E.C.G.

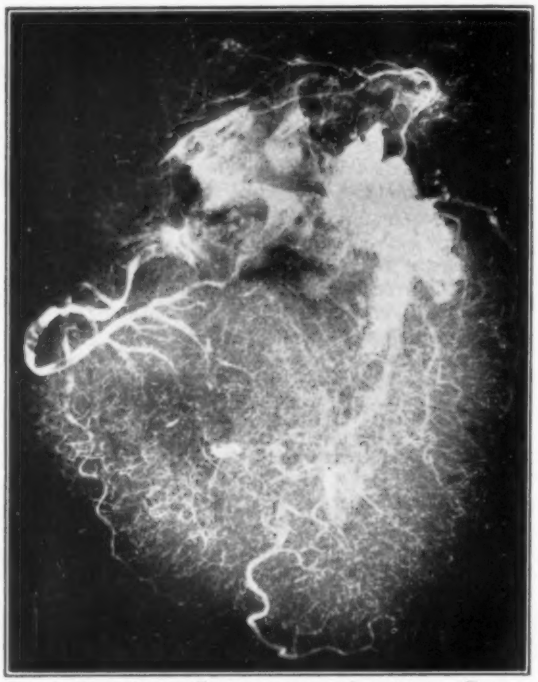

FIG. 6.—Extensive small-artery anastomotic pattern. From a man of 53 with an ischaemic E.C.G. but no chest pain.

indicative of ischaemia, was found in the remaining six, of whom three had ischaemic E.C.G.s: in these three the anastomotic network was particularly dense (Fig. 6).

Discussion

Before accepting that the abnormal tracings were caused by myocardial ischaemia, all other factors must be considered. ST segment and T-wave changes produced by ventricular hypertrophy, pericarditis, and electrolyte disturbance (particularly hypokalaemia) were excluded by selection of cases; the absence of cardiac lesions was confirmed at necropsy. Right bundle-branch block and transient changes from anaemia have not been included in the ischaemic total. Other possibilities to be taken into account are the effects of age, extracardiac disorders, and physiological factors.

The effect of *age* alone cannot be assessed during life, since coronary atheroma cannot be excluded. Olbrich and Woodford-Williams (1953) found the only changes constantly attributable to age were increased duration of the QRS complex and diminished amplitude of T waves in the precordial leads. We have not included such minor deviations in our ischaemic total. Silver and Landowne (1953) noted depression of ST segments of up to 1.5 mm. after exercise in the aged; this might well be due to ischaemia.

Diseases of other organs are known sometimes to produce transient inversion of T waves, and Levine (1953) lists, among other causes, shock, anoxia, carbon monoxide poisoning, pulmonary embolism, acute infections, intracranial diseases, and endocrine disorders. In our series these conditions were excluded, and the patients with acute infections were studied after recovery.

Physiological alterations of the E.C.G. resembling those due to coronary disease may be produced by

meals (Gardberg and Olsen, 1939; Simonson and Keys, 1950), by emotional disturbance and by smoking (Gardberg and Rosen, 1957; Rosen and Gardberg, 1957), and by respiration (Gazes, 1950; August *et al.*, 1958). Rochlin and Edwards (1954) attribute this effect of meals to redistribution of potassium consequent upon carbohydrate absorption, and consider that only a large carbohydrate meal would be likely to produce such effects. Our tracings were usually recorded before meals, or after a small amount of food only. Gardberg and Rosen (1957) attribute ST and T changes induced by exercise, emotion, or smoking in healthy subjects to an alteration in the gradient of repolarization from tachycardia. In our series such changes were not assessed during tachycardia. Respiratory variations are recognizable by cyclic variations in the tracing, and these have been allowed for in assessing our results. In addition, the abnormal pattern has persisted in the cases followed annually so far, which is against transient physiological alterations. Furthermore, at necropsy the cases with abnormal E.C.G.s were found to show the vascular pattern associated with myocardial ischaemia (Shillingford, 1950; Fulton, 1956), and the absence of other pathological causes was confirmed.

Taking all the evidence into consideration, we conclude that the electrocardiographic abnormalities found in our cases represent myocardial ischaemia without referable symptoms or other signs. It is well known that coronary atheroma, with narrowing, occlusion, and myocardial fibrosis, are not uncommonly found at necropsy in this age-and-sex group when there have been no symptoms during life; it is not surprising that this is also occasionally reflected by the E.C.G. Our figure of 12% is similar to that of 10% found by Acheson (1957) in younger men; and it has been shown that marked coronary atheroma can be found from the age of 20 in men of Western races (Enos *et al.*, 1955).

Our findings therefore confirm that abnormal E.C.G.s due to myocardial ischaemia are not rare among middle-aged men without cardiac pain. It follows that the recording of an ischaemic tracing in a patient *with* chest pain does not inevitably mean that the pain is of cardiac origin. In cases of hiatus hernia or spinal disease an abnormal tracing could well mislead the physician. This re-emphasizes the necessity for careful assessment of the history and clinical data in all cases of chest pain. As stated earlier, patients with normal E.C.G.s may none the less be correctly regarded as cases of ischaemic heart disease because of other relevant considerations. The clinician should similarly feel free to exercise his judgment when the E.C.G. is abnormal in a patient whose pain is not really suggestive of a cardiac origin. To quote East (1950): "The cardiogram is only one detail in the clinical picture—its importance can be assessed only by seeing the picture as a whole."

Serum Lipoproteins

The serum lipoproteins were studied in 59 patients, of whom nine had ischaemic E.C.G.s. The method used was paper electrophoresis as described by Dangerfield and Smith (1955). They observed an abnormal band migrating ahead of beta-lipoprotein (Fig. 7) in most patients with myocardial infarction. Subsequent studies on larger series of patients have confirmed the association of this "pre-beta-lipid" band with myocardial infarction (Besterman, 1957; Smith, 1957), and it has been demonstrated by Smith (1957) that it is roughly equivalent to the ultracentrifugal Sf 20–100 group of Gofman *et al.* In this investigation the presence of moderate or large amounts of the pre-beta-lipid band

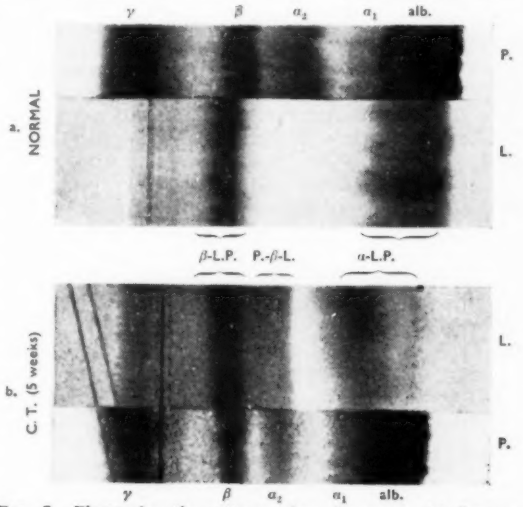

FIG. 7.—Electrophoretic patterns given by serum (*a*) from a normal woman, and (*b*) from a patient five weeks after myocardial infarction. P., part of strip stained for protein; L., part of strip stained for lipid; alb., albumin; α-L.P., alpha-lipoprotein; β-L.P., beta-lipoprotein; P.-β-L., pre-beta-lipid.

was used as the criterion of lipoprotein abnormality. The band was assessed quantitatively by the score system described by Smith (1957) and divided arbitrarily into three categories—minimal (score 0–1½), moderate (score 2–4), and large (score 4½–7).

The lipoprotein findings were compared with those in two other groups of men within the age range 50–70: 71 with known ischaemic heart disease and 104 in apparent good health. These last two groups have previously been reported by Smith (1957). They were compared also with the distribution of the pre-beta-lipid band in 232 healthy men aged 20–84.

Results

The type of lipoprotein abnormality looked for is illustrated in Fig. 7. The prevalence of minimal (score 0–1½), moderate (score 2–4), and large (score 4½–7) pre-beta-lipid bands in the 59 hospital in-patients without chest pain is shown in Table III, and compared with cases of established ischaemic heart disease and with healthy men in the same age range. A moderate pre-beta-lipid was found in approximately half of each group. A large pre-beta-lipid band was found in 10%

TABLE III.—*Pre-beta-lipid Level in Various Groups of Patients*

	Group of Patients	No.	Aver. Age	Pre-Beta-Lipid Level			
				Aver. P.-β-L.	Min.	Mod.	Large
Patients in electrocardiographic series	Normal E.C.G.	50	60	2·5	36%	54%	10%
	Ischaemic ,,	9	63	3·8	11%	55½%	33½%
Patients with coronary disease	Acute myocardial infarction examined within 3 months of the attack*	43	59½	4·0	7%	51%	42%
	Angina with no history of infarction	28	59	3·6	7%	57%	36%
Controls	Healthy men aged 50–69	104	60	1·5	53%	44%	3%

* From Smith (1957).

or less of the hospital patients with no pain and normal E.C.G.s, and in the healthy men; it occurred in 33% of the patients without pain but with ischaemic E.C.G.s, a figure comparable to the 36–42% in established cases of cardiac infarction and angina.

Discussion

To provide a standard of comparison against which the lipoprotein findings can be assessed, the distribution of the pre-beta-band in 232 healthy men aged 20–84 years is shown in Fig. 8; this shows the average

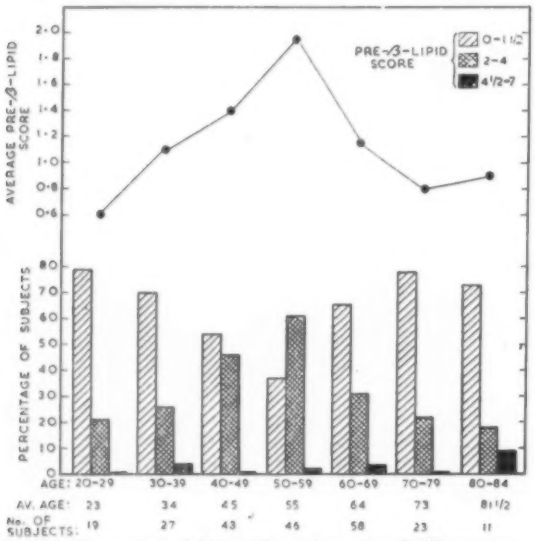
AVERAGE PRE-β-LIPID SCORE
PRE-β-LIPID SCORE
0–1½
2–4
4½–7
PERCENTAGE OF SUBJECTS
AGE: 20–29 30–39 40–49 50–59 60–69 70–79 80–84
AV. AGE: 23 34 45 55 64 73 81½
No. OF SUBJECTS: 19 27 43 46 58 23 11

FIG. 8.—The pre-beta-lipid level in healthy men of different ages. The histogram shows the distribution of minimal, moderate, and large pre-beta-lipid bands in successive decades, and the graph shows the average pre-beta-lipid score.

pre-beta-lipid score and the percentage with minimal, moderate, and large pre-beta-lipid bands in different decades. There is marked variation with age, and, although the lipoprotein pattern is normal in 80% of men in their twenties, a moderate pre-beta-lipid is found in over 60% of men in their fifties; a large pre-beta-lipid is, however, very rare in healthy men of any age, and was found in only six (2½%) out of the whole group.

An examination of the results in Table III suggests a number of points. Firstly, a moderate or large pre-beta-lipid was found rather more often in the hospital patients with normal E.C.G.s than in healthy men of comparable age. We have observed a large pre-beta-lipid band in a number of unrelated conditions, including dermatomyositis, gastric ulcer, carcinoma of the bronchus, carcinoma of the bladder, and pulmonary tuberculosis, but the findings are not consistent; it seems probable that where there is marked metabolic disturbance the lipoprotein patterns may also be disturbed, and this must be borne in mind in their interpretation. Secondly, a *moderate* pre-beta-lipid band occurs in about half the men in every group; thus, although it may have some significance in relation to atheroma, its presence does not correlate with clinical coronary disease. Thirdly, a large pre-beta-lipid band occurs in about one-third of patients with electrocardiographic evidence of myocardial ischaemia whether or not there be referable symptoms, although the symptomless group is not really large enough for comparison. Considering this finding in relation to Smith's (1957) observation of a striking increase in pre-beta-lipid *after* myocardial infarction, we are tempted to speculate whether a *large* pre-beta-lipid band (roughly equivalent to the Sf 20–100 group of Gofman *et al.*) may be associated with myocardial damage rather than with coronary atherosclerosis.

We intend to continue to follow up the surviving patients in the group without chest pain and to report further on any subsequent development of clinical coronary disease in relation to the electrocardiographic and lipoprotein findings.

Summary

Electrocardiograms were recorded in 100 men aged between 50 and 80 years, none of whom had chest pain or any evidence of cardiac disease. Twelve tracings showed evidence of myocardial ischaemia. This emphasizes the need for care in using electrocardiography in the assessment of chest pain, which is not necessarily of cardiac origin even though the tracing be abnormal.

In 59 of these men, including nine with abnormal tracings, the serum lipoproteins were examined by paper electrophoresis for the presence of an abnormal pre-beta-lipid band (which corresponds approximately with the Sf 20–100 fraction of Gofman *et al.*). The results were compared with those in known cases of ischaemic heart disease. A moderate quantity of abnormal lipid was found in a similar percentage of both groups and did not correlate with clinical coronary disease. A large abnormal band did, however, appear to correlate with electrocardiographic evidence of myocardial ischaemia.

We are indebted to the physicians of St. Bartholomew's Hospital, and to Sir James Paterson Ross, for permission to study patients under their care. We are also indebted to Dr. R. Acheson, of the Moyne Institute of Preventive Medicine, Trinity College, Dublin, for electrophoretic patterns on 51 men aged 65–85; without this valuable contribution sufficient material in this age group could not have been collected. This work was carried out while one of us (D. W.) was holder of the Cooper and Cattlin Research Scholarships at St. Bartholomew's Hospital. Part of the lipoprotein work was done in the Department of Chemical Pathology, St. Bartholomew's Hospital, and part in the Courtauld Institute of Biochemistry, with the support of the Medical Research Council.

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ATROPINE CIGARETTES IN ASTHMA AND EMPHYSEMA

BY

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Before the advent of adrenaline as the main agent for immediate relief from an acute attack many asthmatics relied on burning a powder made from leaves of stramonium, belladonna, and/or hyoscyamus and inhaling the smoke. This was said to bring relief in some cases. This remedy is no longer in official use, although in Germany, for instance, "asthma cigarettes" consisting of powdered stramonium leaves can be bought in every chemist's shop, and it may be assumed that they are widely used without medical prescription. Current textbooks of pharmacology hardly mention atropine and hyoscyamine, the active principles in these powders, in the treatment of asthma.

One reason for this apparent neglect may be the observation that atropine given systemically has no appreciable effect in asthma. Locally, it is still used in aerosols, usually as atropine methonitrate, which is found in a concentration of 0.1% in the *British National Formulary* preparation of neb. adrenal. atrop. co. and in neb. isoprenal. co. as well as in many proprietary aerosol solutions. It is doubtful whether it has any anti-asthmatic effect in these preparations. I have not observed any benefit in patients using atropine methonitrate 0.1% as an aerosol (unpublished observations). If these preparations are inhaled frequently, however, they cause dryness of the mucous membranes. Their therapeutic inefficacy has also been mentioned by Wolfer (1956). This apparent discrepancy between the effects of wet atropine aerosol and atropine smoke made it desirable to reinvestigate the problem. This paper is concerned with the effect of *atropine smoke* on lung function in asthmatic and emphysematous patients.

Method

As the amount of atropine and hyoscyamine in commercial stramonium cigarettes is likely to vary, atropine cigarettes were prepared by the method of Holmstedt and Wallén (1959). Tobacco containing little nicotine (less than 0.06%) was used, and amounts of atropine sulphate were added which on burning the tobacco in the main stream,* according to the authors, left a residue of atropine in cigarettes of two different strengths, so that either 0.5 mg. or 1.45 mg. was inhaled by the patient. The patients were instructed to hold their breath after inhalation for at least two or three seconds. According to Baumberger (1923) and Ervenius *et al.* (1958) a much higher proportion of smoke particles is retained with this method than with ordinary breathing. Baumberger found that with ordinary "puffing" 67% was retained and with inhaling 88%; Ervenius *et al.* found that with "superficial" smoking 19% was retained and with inhaling 80%.

The rhythm of the smoking and the total time required for one cigarette were left to the patient, except that he was instructed not to hurry. The vital capacity (V.C.) was used as test of lung function. This method has stood the test of time, and in my opinion is as good an indicator of bronchial obstruction as any of the more fashionable methods, as, for instance, the timed V.C. and the M.B.C. (maximum breathing capacity). The latter methods have, particularly in asthmatics, the great disadvantage of increasing bronchial obstruction either by hyperventilation or by forced expiration from the maximum inspiration point. Many of our subjects acquired such a skill in breathing with the recording spirometer that their basal values varied only within a range of 50 ml. Such uniform results can be achieved only if enough time is allowed between estimations (in emphysematous subjects one and a half to two minutes) and if expiration from maximum inspiration point is avoided.

The patients taking part in the present investigations suffered from bronchial asthma or from emphysema. As is well known, long-standing bronchial asthma leads to a state of hyperinflation of the lungs commonly regarded as equivalent to emphysema. In this study the term "bronchial asthma" denotes chronic bronchial asthma of allergic or infective origin, whilst by emphysema is meant increasing breathlessness on exercise beginning with or without cough and proceeding (with rare exceptions) to moderate or severe incapacity from dyspnoea and bronchitis with hypersecretion, without primary heart disorder. Whether anatomical emphysema was present in any of these cases is uncertain. It is certain that bronchial obstruction and hyperinflation were present in all of them and that the hyperinflation was somewhat less reversible in the cases labelled emphysema.

Twenty-three subjects were tested with 1.45-mg. atropine cigarettes in 48 experiments, and 16 with 0.5-mg. cigarettes in 24 experiments. Ten patients were tested with both kinds of cigarettes. The procedure was as follows. The V.C. was recorded, in the sitting position, with a low-resistance spirometer and constant oxygen replacement, so that the tracing of the tidal air remained horizontal. The subject was asked to exhale as much as possible and then to resume normal breathing. After a few further normal breaths maximum inspiration was recorded. This procedure in most cases avoids the distension phenomenon first described by Christie and McIntosh (1934). This is a decrease of the V.C. caused by additional bronchial obstruction due to the high intrathoracic pressure resulting from the patient's pressing out from the maximum inspiration point.

When the patient had been trained in this method of recording the V.C. three recordings were taken. If they did not differ by more than 150 ml. their mean was used as the baseline; if they did, the highest reading was used, or the two highest if these were not more than 150 ml. apart. The subject then smoked the cigarette. The V.C. was again recorded three times: immediately after the cigarette had been smoked; again 10 to 15 minutes later; and then at varying intervals, in a few cases up to several hours. In some cases, particularly in those in which the V.C. increased to an unexpected degree after the cigarettes, the subject was on a later occasion, as a blind control, given a cigarette of the same kind without atropine.

In some further experiments ordinary commercially available asthma cigarettes were smoked which contained, according to the declaration of the manufacturers, nothing but folia stramonii. In other experiments a 0.5% solution of atropine sulphate with a

*"Main stream" smoke is the smoke which is inhaled by the smoker, in contrast to the smoke leaving the cigarette between the puffs.

little glycerin added was aerolized by the scrubber nebulizer of Dautrebande (1951), which, according to this author, delivers homogeneous aerosols of a particle size of 200–400 Å. The subject took 20 deep breaths of this aerosol, which was nebulized at a pressure of 0.3 atmosphere; this took about 3 minutes. It was observed that the amount of fluid lost from the scrubber during this procedure was about 150 mg., containing 0.75 mg. of atropine. Only a part of this amount is retained by the subject, as some of the aerosol is deposited in the tubes leading to the mouthpiece, and some of it is inhaled and exhaled again. If it is assumed that the subject has retained less than half of the total produced by the scrubber, this would be about 0.3 mg. of atropine.

As a comparison, a commercial nebulizer was used to produce a 0.5% atropine sulphate aerosol with a varying droplet size and a mean diameter of 2μ. The inhalation of this aerosol for 10–30 seconds had proved ineffective several years ago; in the present experiments it was used for periods up to three minutes.

Results

The results are given in Table I. In the great majority of cases the V.C. increased after the smoking, often by a substantial amount. This increase varied considerably. It was absent or negligible only in those cases in which the basal value was normal at the time of the experiment—that is, where the clinical condition of the patient was satisfactory and where it was not possible to increase the V.C. by other means (isoprenaline or ephedrine). Under those circumstances a further increase of the V.C. could not be expected from atropine (or from any other drug); these cases have been included in Table I, but not in our evaluation of the atropine effect. The increases of the other experiments range from 5% to 48%, and in 52 of the 62 experiments evaluated the increase was 10% or more. We have arbitrarily assumed increases from 5% to 9% to be "negative," although some of the small increases may well represent an atropine effect. Blank cigarettes did not change the V.C. more than ±3%. A decrease of the V.C. occurred in only two patients in whom the smoke induced cough with a subsequent fall of the V.C., from which they slowly recovered. These experiments have been omitted from Table I.

The increase often became noticeable immediately after the smoking—that is, after three to five minutes—but in only five of the experiments was the maximum increase reached at that time. In most cases (26) the maximum increase was reached after 15 to 30 minutes, in 14 experiments after 35 to 60 minutes. In seven experiments the maximum increase occurred only after one hour. The highest increase after 1.45 mg. atropine was 48%, after 0.5 mg. 34%. There were six "negative" results with 0.5 mg. and four with 1.45 mg. Both atropine doses were given to six patients (Table II). In all of them 1.45 mg. of atropine had a slightly but definitely stronger effect than 0.5 mg., the mean increase of the V.C. being 17% against 12%. The average maximum increase in all experiments, however, was equal for both doses (about 18%). In many cases the patients commented spontaneously on their increased ease of breathing.

The duration of the increase, which varied considerably, is shown in Figs. 1 and 2. At 90 minutes the increase was fully maintained, but after three hours it had mostly disappeared. In Fig. 1 an experiment with a maximum increase of 9% is included, as the time course of the increase and decrease of the V.C. is typical of an atropine effect.

TABLE I.—*Percentage Increase of Vital Capacity After Atropine Cigarettes*

Subj.	V.C. (cm.³) Before	Dose of Atropine (mg.)	Increase of V.C. after Minutes: 3–5	15–25	40–60	120	180	Remarks
Pl ..	2,505	1·45	6%	8%	16%			E
Pl ..	2,570	1·45	6%	13%	18%	(90') 0%		
Pl ..	2,485	1·45	11%	18%	16%			
Pl ..	2,440	1·45	10%	15%				
Pl ..	2,370	0·5	8%	14%				
Pl ..	2,215	0·5	6%					
Wi ..	3,550	1·45	0%	1%	6%	(95') 12%	(5 hr) 0%	E
Wi ..	*4,030	0·5	0%	—	0%			
Ed ..	*3,220	1·45	0%	0%	4%			E
Ed ..	2,820	0·5	7%	8%				
Teu ..	2,225	1·45	12%	20%				A
Teu ..	2,510	1·45	0%	10%	9%			
Teu ..	2,525	1·45	2%	10%				
Teu ..	*2,755	0·5	—	3%	3%			
Teu ..	2,580	0·5	3%	6%	10%			
Schie	*5,775	1·45	0%	0%				A
Kl ..	3,500	1·45	31%	34%	37%		(5½ hr.) 48%	A
Kl ..	5,360	1·45	13%	14%				(9 hr.) 0%
Els ..	2,455	1·45	8%	14%	26%	26%		E
Els ..	2,530	1·45	9%	12%	16%	(90') 17%		
Els ..	2,250	1·45	13%	20%	30%	16%	12%	
Els ..	2,120	1·45	18%	28%				
Gne ..	*4,230	1·45	0%	0%	0%	(100') 4%		A
Wol ..	2,560	1·45	26%	31%				E
Wol ..	2,875	1·45	16%		31%			
Wol ..	2,960	1·45	18%	20%				
Wol ..	3,170	1·45	11%	13%				
Wol ..	2,915	1·45	17%	30%	—	15%	17%	
Wol ..	2,875	1·45	18%	—	26%			
Wol ..	3,140	1·45	10%		13%	7%	4%	
Wol ..	2,975	0·5	9%	19%				
Wol ..	2,900	0·5	17%		25%			
Schwa ..	1,820	1·45	7%	—	5%	0%		E
Bel ..	1,920	1·45	5%		4%	0%		A
Bel ..	2,075	1·45	0%	9%	—	24%		
Bel ..	*3,100	1·45	0%	0%	—	(80') 0%		
Elix ..	2,640	1·45	3%		10%			A
Elix ..	1,400	0·5	34%	24%	33%			
Oberl ..	2,265	1·45	10%	—	13%			E
Oberl ..	2,175	0·5	—	0%	6%			
Mel ..	3,240	1·45	0%	0%	15%			A
Dr. Br ..	2,420	1·45	7%	5%	3%			E
Haut ..	*4,040	1·45	0%	0%				A
Pie ..	2,365	1·45	21%	28%				E
Pie ..	2,225	1·45	24%	29%				
Pie ..	2,040	1·45	19%	16%				
Pie ..	2,340	1·45	13%				(4 hr.) 0%	
Pie ..	1,895	0·5	10%		22%			
Pie ..	2,425	0·5	13%	15%				
Pie ..	2,225	0·5	11%	17%				
Pie ..	2,640	0·5	7%	—	15%			
Pie ..	2,425	1·45	12%	19%				
La ..	2,200	1·45	11%		28%			E
Wo ..	1,400	1·45	31%					E
Wo ..	1,770	1·45	21%	33%	—		(205') 19%	(8 hr.) 0%
Wo ..	2,035	1·45	13%	19%	(70') 20%	14%	(205') 22%	
Wo ..	1,710	1·45	10%	—	—	13%		
Ra ..	*3,035	1·45	0%	0%				A
Ra ..	*3,125	0·5	3%		0%			
Ra ..	2,605	1·45	9%	6%	—	3%		
Sk ..	1,745	1·45	14%	12%	—	(95') 14%	5%	E
Sk ..	1,790	0·5	—	6%	9%	(100') 6%	0%	
We ..	3,080	1·45	0%	—	14%	25%	(90') 13%	E
Dall ..	2,185	1·45	19%	—	18%			A
Qu ..	2,300	0·5	6%	—	12%	(85') 13%		E
Bross ..	3,555	0·5	3%	—	7%	5%		A
Ku ..	2,400	0·5	7%	—	0%			E
Kum ..	3,380	0·5	20%	27%				E
Lü ..	2,590	0·5	3%	19%				E
Lü ..	2,420	0·5	14%		23%			
Lü ..	*3,190	0·5	0%	2%				
Lin ..	1,730	0·5	0%	15%	23%		(165') 2%	E

*Normal basal value. E = Emphysema. A = Asthma. Values given between 2 adjacent columns were obtained at intermediate times.

In some experiments ephedrine was given first and the resulting increase of V.C. recorded. When it had reached what was assumed to be its peak an atropine cigarette was smoked in order to test whether this substance had an additional effect. In other experiments this order was reversed. The results (Table III) show that in many cases the V.C. increased after ephedrine and after atropine independently of the order in which they were given.

The results with cigarettes containing stramonium were similar to those with the atropine cigarettes (Table IV). The inhalation of the 0.5% wet atropine aerosol with the Dautrebande scrubber also caused an increase in V.C. (Table V). When this was compared with the effect of a 0.5% atropine aerosol from an ordinary commercial nebulizer, a one-minute continuous respiration showed an increase of the V.C. in three experiments, whilst there is very little change in the other two. When, in those two experiments, the subject smoked in addition an atropine cigarette the increase of the V.C. became substantial. When, however, in five other experiments the inhalation period was extended to three minutes, the increase in V.C. was substantial and comparable to that seen after inhaling from the scrubber and after atropine cigarettes (Table V).

TABLE II.—*Means of Greatest Increase in V.C. in Patients Who Had Both Doses of Atropine*

Subj.	0·5 mg.			1·45 mg.		
	No. of Obs.	Mean Initial V.C. (cm.³)	Mean Increase	No. of Obs.	Mean Initial V.C. (cm.³)	Mean Increase
Pl ..	2	2,300	10%	4	2,500	17%
Teu ..	1	2,580	10%	3	2,500	17%
Wol	2	2,940	22%	7	2,920	26%
Oberl	1	2,175	6%	1	2,265	10%
Pie	4	2,295	17%	5	2,280	22%
Sk ..	1	1,790	9%	1	1,745	14%

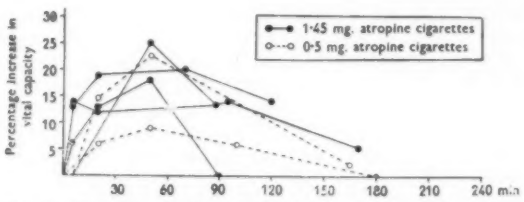

FIG. 1.—Duration of effect of atropine smoke on vital capacity.

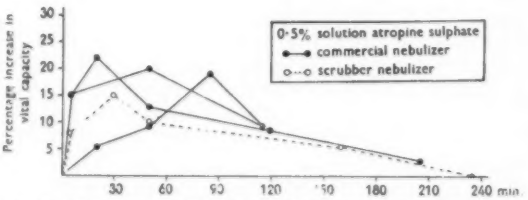

FIG. 2.—Duration of effect of atropine aerosol on vital capacity.

TABLE IV.—*Cigarettes with Folia Stramonii*

Subj.	V.C. (cm.³) Before	Doses	Increase of V.C. After ‡		
			3–5 min.	15–25 min.	30 min.
Wol ..	3,050	1 cig. stram.	9%	17%	
Ku ..	3,200	,, ,, ,,	17%	23%	
Pie ..	2,470	,, ,, ,,	15%	22%	
Lin ..	1,395	,, ,, ,,	8%	14%	
Pl ..	2,120	,, ,, ,,	14%	13%	
Pl ..	2,440	*1 cig. atr. 1·45	18%	26%	
		1 cig. atr. 1·45	11%	—	15%
		†1 cig. stram.	11%	—	19%

* This atropine cigarette was smoked 19 minutes after beginning the experiment.
† This stramonium cigarette was smoked 30 minutes after beginning the experiment.

Discussion

The present results leave no doubt that the inhalation of atropine smoke has a beneficial effect on lung function in bronchial obstruction. This effect is a little greater with 1.45 mg. than with 0.5 mg. and often lasts several hours; unpleasant side-effects, like cough, have been rare, although it is possible that they will increase with frequent use of this remedy. This positive result accords well with the animal experiments of Bouaziz (1954), who found that smoke containing atropine antagonized bronchial spasm induced by acetylcholine (though it was less potent in histamine-induced spasm). The present results show that the low esteem in which current textbooks hold atropine in the treatment of asthma is not justified and that atropine smoke has a definite place in the treatment of asthma and emphysema. This is important, because the therapeutic range of other available substances, particularly in emphysema, is limited. Ephedrine, the most valuable substance, becomes ineffective when given more than twice daily because tolerance develops (Herxheimer, 1946), and is contraindicated in the evening because of its central stimulant action. Moreover, it often has unpleasant side-effects. It is therefore most desirable to have a drug with an anti-spasmodic effect which lacks the disadvantages of ephedrine and can be given when ephedrine is contraindicated or in order to increase its effect.

The present results accord well with the reputation that stramonium enjoyed with the medical profession

TABLE III.—*Ephedrine and Atropine given in Succession*

Subj.	V.C. (cm.³) Before	Doses	V.C. After							
			3–5 min.	15–25 min.	40–60 min.	Doses*	73–75 min.	85–95 min.	110–130 min.	2 hr.
Quo†	1,990	75 mg. eph. oral	—	—	1,985	1 cig. atr. 1·45	2,285	2,275	2,420 2,340	
Quo†	2,120	125 ,, ,, ,,	—	—	(72') 2,100	1 ,, ,, 1·45	2,395	2,425	2,505	
Quo†	2,405	100 ,, ,, i.v.	2,355	—	2,325	1 ,, ,, 0·5	2,730	2,850		
Sk† ..	1,670	400 ,, methyleph. i.v.	1,620	—	1,610	1 ,, ,, 1·45	1,800	2,020		
Ed ..	2,705	1 cig. atr. 1·45 mg.	3,000	2,905	3,020 —	50 mg. eph. oral		—	— 3,040‡ 3,170 (90') 3,065	
Kl ..	3,220	50 mg. eph. i.v.	4,430	—	4,820	1 cig. atr. 0·5	5,230	—	6,060	
Schw	1,780	75 mg. eph. oral and 50 mg. i.v.	1,890	1,975	—	1 ,, ,, 1·45	1,905	1,785	2,000	
Wol ..	2,810	100 mg. methyleph. i.v.	3,050	—	3,075 —	1 ,, ,, 1·45	3,600	—	—	
Lü ..	2,050	150 mg. eph. i.v.	2,420	—	—	1 ,, ,, 1·45	2,460	2,590		
Pl ..	1,995	760 mg. methyleph. oral	—	—	2,195	1 ,, ,, 0·5	2,440	—	—	
Lin ..	1,420	50 mg. eph. oral	—	—	1,555	1 ,, ,, 1·45	1,570	1,860		
Ra ..	2,060	100 ,, ,, ,,	—	—	2,590	1 ,, ,, 1·45	2,735	2,765	2,780	
Pie	1,880	1 cig. atr. 0·5 ,,	2,100	—	2,045 —	120 mg. methyl eph. i.v.	2,420			
Lan	2,120	1 ,, ,, 0·5	2,650	—	3,070 —	50 mg. eph. i.v.	3,000	3,160		

*The second drug was given 60-70 minutes after the first. † This subject was refractory to ephedrine. ‡ Close to the normal V.C. of this subject.

TABLE V.—*Effect of Wet 0.5% Atropine Aerosols From Scrubber Nebulizer and Commercial Nebulizer*

Subj.	V.C. (cm.³) Before	Doses	Increase of V.C. After				
			3–5 min.	15–25 min.	40–60 min.	2 hr.	3 hr.
Wo ..	1,815	20 deep breaths 0·5 atropine scrubber nebulizer	15%	22%	13%	(135') 7%	
Pie ..	2,560	" " "	9%	12%	(70') 11%		
Pl ..	2,320	" " "	15%	—	20%	8%	
Wol ..	3,110	" " "	13%	18%			
Sk ..	1,825	" " "	—	5%	8%	(85') 19%	
Tre ..	1,850	" " "	—	6%	2%		
Haus ..	2,400	" " "	0%	12%			
Ra ..	2,675	2 × 12 deep breaths 0·5% atr. scrubber nebulizer	7%	13%			
Pie ..	2,360	1 min. 0·5% atr. comm. nebul.	8%	15%	10%		(165') 5%
Wol*	3,015	1 min. 0·5% atr. comm. nebul.	5%	7%	4%		
Sk* ..	1,745	60 min. later 1 cig. atr. 1·45	15%	18%		11%	
		1 min. 0·5% atr. comm. nebul.	5%	—	0%		
Pl ..	2,590	60 min. later 1 cig. atr. 1·45	14%	12%	—	(95') 14%	
		3 min. 0·5% atr. comm. nebul.	7%	14%			
We ..	3,300	" " "	5%	—	22%		
Kum ..	3,795	" " "	10%				
Sk ..	1,565	" " "	14%	2%	4%		
Wo ..	1,560	" " "	19%	17%			

* Smoked an atropine cigarette 60 minutes after having the wet aerosol.

100 to 150 years ago. It is a matter for conjecture why it has since fallen into disrepute. Finnegan (1950) has given a detailed review of this development. It appears that the use of stramonium leaves in Europe dates back to the beginning of the nineteenth century. Favourable reports were published in 1811 and in the years that followed (Christie, 1811; English, 1811; Hageweisch, 1813; Miquel, 1836; Mirande, 1837; and others). Between 1890 and 1930 the literature does not seem to mention stramonium as a valuable remedy.

More recently, with the appearance of many textbooks of allergology, varied opinions have been expressed, although mostly with little supporting evidence. Thus Walzer (1931), Rackemann (1931), Vaughan (1934), Crisp (1945), and Cooke (1947), mention stramonium powder as a beneficial drug, though in a rather non-committal way, whereas Rowe (1937), Feinberg (1934), Bray (1934), Tuft (1937), Unger (1945), Urbach and Gottlieb (1946), Carryer *et al.* (1946), and Alexander (1947) are critical of its use. The latter authors think that the repeated use causes irritation of the air passages, and some of them attribute the beneficial effect mainly to the potassium nitrate often mixed with powdered stramonium leaves. Moreover, Swineford (1937) observed a case of asthma in which sensitivity to the powder had developed during the five years of its continued use. This critical attitude does not seem fully justified. If indeed such side-effects should occur through continued use of atropine smoke, its use must be restricted accordingly. But even its restricted use seems to be a valuable addition to the group of therapeutically effective substances.

The beneficial effect is, of course, not limited to atropine cigarettes: it occurs, for the same pharmacological reasons, with cigarettes made from stramonium leaves and also with wet atropine aerosols, provided that the droplets are small enough to penetrate into the finer bronchioli. It is probable that the very small particle size which permits penetration into the alveolar ducts and possibly into the alveoli is essential for the beneficial effect of the atropine smoke as well as of the wet aerosols. The negative result of earlier observations with wet aerosols is probably explained by the smaller amount of atropine in the aerosol used and by the shorter duration of its application, possibly also by the preponderance of larger particles not able to penetrate into the finer air passages.

There are thus three different methods for the local application of atropine in very small particles: the stramonium cigarette, the atropine cigarette, and the wet aerosol. Compared with the first, the atropine cigarette has the advantage of presenting an accurately known dosage. The wet aerosol has the advantage that no irritation through other substances present in smoke can occur. Its practical disadvantage is that the apparatus for the production of such fine aerosols is a little cumbersome and cannot easily be used in daily life. The atropine cigarette, however, is easy to use, particularly if the tobacco employed as carrier is freed from irritating substances and has an inoffensive smell.

The dosage of atropine used in the present experiments requires comment. As the cigarettes producing 0.5 mg. of atropine had an effect similar to that of the stronger ones, it must be assumed that this amount was effective. As some of the smoke is exhaled by the patient, and as the retained particles, according to Ervenius *et al.* (1958) represent, with deep inhalation of the smoke, not more than 80% of the total main stream smoke, the effective amount of atropine appears to be less than 0.4 mg. How much less is not known, as the amount uselessly deposited in the upper respiratory passages is unknown. With the wet atropine aerosol, the total amount of atropine retained may be similar.

On the other hand, oral atropine in man has no effect in bronchial asthma even if it is given in amounts of 1 mg. It is probable that larger doses would be effective (Cullumbine *et al.*, 1955), but their side-effects limit their use. In the guinea-pig, which tolerates large amounts of atropine, high doses (Armitage *et al.*, 1952) have a certain protective effect against the anaphylactic micróshock which closely resembles bronchial asthma; and in the isolated organ, the tracheal chain, atropine also counteracts bronchial spasm (Schild, 1936).

From this it appears that an effect can be achieved with very much smaller doses applied locally than by systemic administration. This local effect is achieved in the smaller bronchi, the alveolar ducts, or the alveoli themselves. Whether this is mediated through nervous elements or whether it is a direct effect on the bronchial muscle is not clear. It can hardly be a systemic effect: the small amount of effective substance points against it; moreover, the pulse rate in many of our subjects did not increase under the influence of the atropine smoke, and the maximum increase observed was six beats a minute. Mydriasis was not seen during the experiments (it may have appeared later), and only one subject complained of dryness of the mouth.

It is well known that the mechanism of action is different from that of ephedrine. I have seen cases in which large doses of ephedrine were quite ineffective, whereas atropine was effective, and in a number of

experiments (Table III) it has been shown that the effect of both substances is complementary.

Summary

Atropine administered locally in cigarette smoke or wet aerosols increases the vital capacity and gives a feeling of relief in cases of mild or moderate chronic asthma and emphysema.

The effective dose probably lies below 0.4 mg. of atropine sulphate.

Atropine is easily administered by smoking. This method of administration is simple; as the dosage can be accurately controlled, it is preferable to that of wet aerosols and of stramonium cigarettes.

I am indebted to Dr. B. Holmstedt, Stockholm, and Dr. Andrew Herxheimer, London, for their advice, and to the Vitrum Company, Stockholm, 12, which supplied the atropine cigarettes. Messrs. E. Merck & Co., Darmstadt, kindly supplied methylephedrine in tablets and solution.

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The Nutrition Research Laboratories of the Indian Council of Medical Research have just issued their annual report for 1957–8. Studies on proteins and protein malnutrition, iron metabolism, and vitamins are included. There are sections devoted to field investigations in some Nilgiri tribes; studies in human lactation; and the growth and physical development of Indian children. A brief account is given of the education and advisory work done by the Laboratories (*Annual Report for 1957–8*, Nutrition Research Laboratories, India Council of Medical Research).

TREATMENT OF PILONIDAL SINUS BY EXCISION AND PRIMARY CLOSURE*

BY

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In the past seven years the cure of 442 cases of pilonidal sinus has been undertaken in the United Birmingham Hospitals, a teaching group where it is to be expected that a complete spectrum of cases and operations is to be seen besides operations of a highly specialized nature requiring team-work.

Except in those instances where the patient presents with an acute abscess for incision and drainage, the track and ramifications of the sinus must be excised. There are two opposing views on what should be done with the wound after this: should it be left open to be allowed to granulate from the bottom or be closed by primary suture? Textbook and practice have often given the impression that the former method is the one of choice on the grounds that the sinus is chronically infected, that the whole area is a "dirty" one, and that the frequent multiplicity of sinus openings prevents the surgeon from obtaining and retaining primary closure of the wound. A random sample of the records of 72 cases treated in one of the two teaching hospitals here shows that 33 wounds were allowed to granulate and 39 were closed by primary suture (46.5% : 53.5%).

If the wound is allowed to granulate, the patient must be resigned to a longer stay in hospital, time in a convalescent hospital, and an extended period off work, with daily dressings carried out by a district nurse. The open wound is unpleasant, the scar is liable to excoriation, and recurrence, for which the pilonidal sinus is notorious, is still possible. Of the 33 cases mentioned above, four recurred. Of the 39 cases of excision and closure, three recurred.

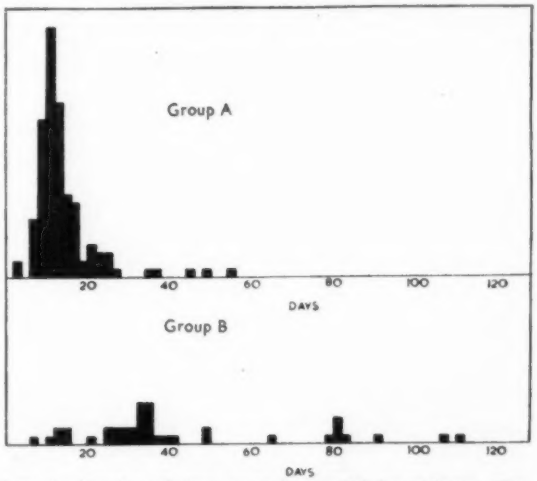

FIG. 1.—Number of days spent in hospital by patients. The majority of group A cases (after excision and primary suture) are sent home with wounds healed. The early discharges in group B patients are sent out of hospital with open wounds, which are dressed in a convalescent hospital or at home by a district nurse.

When careful attention is paid to technique, success from primary suture may nearly always be achieved

*Read to the Section of Surgery at the Annual Meeting of the British Medical Association, Birmingham, 1958.

and the patient is able to return home and to work in the minimum time with a clean and comfortable wound.

It so happened that the group of surgeons working together in the wards of the professorial surgical unit favoured excision and closure, and of 118 patients performed it on 112 (95%:5%). Of these 112 patients, 72 were males, and 40 were females. The length of stay in hospital until the wound was healed was in most cases 10 to 14 days, and home was the usual method of disposal. This point is shown graphically in Fig. 1, which also portrays the length of stay of 39 cases in which the wound was left open and where disposal was usually to convalescent hospital or home for daily dressings. Instances where delay or failure in healing of the sutured wounds occurred are also apparent. In seven cases there was a slight delay in healing, and in four cases the wound did not heal by first intention and fell open when the sutures were removed. Haematoma formation was the cause of this. Out of the 112 cases, there were 11 recurrences (one in a woman and 10 in men), but this rate is no higher than that already given for the "open" cases.

Operative Technique

The following are personal notes, and in detail do not apply to all the cases reported on.

Pre-operatively the patient is given clear glucose fluids on the day before operation, and where possible a low-residue diet for two days before that. An aperient and a soap enema are given, and the skin is prepared by twice-daily baths and swabbing with spirit and chlorhexidine ("hibitane") solution (0.5%). A close shave is essential, since the presence of short hairs on each side of the natal cleft encourages growth into the cleft before the wound has healed.

Under intratracheal anaesthesia the patient is put into a flexed-prone position (Fig. 2). The buttocks are held apart by plaster strips anchored to the table. The skin is prepared with chlorhexidine solution. One of the principles of the excision is not to remove any more tissue than is absolutely necessary, and to this end the injection of indigocarmine into the primary opening of the sinus is most helpful. The dye stains and outlines all the ramifications of the sinus, and, provided the surgeon keeps his excision well clear of any such stained tissue, a successful removal is achieved. Most commonly, the elliptical incision which is used lies in the long axis of the body, but if the secondary openings are displaced to one side it is better to use a curved "boomerang" incision so that a flap is formed which can easily be rotated round to afford complete closure without tension (Fig. 3). The size and thickness of this flap depends upon the volume of tissue affected, and in the extreme case a musculo-fascial flap is made.

FIG. 2.—The flexed-prone position. The buttocks are held apart by strapping. The knees are flexed by resting the lower legs on a pillow strapped to the operating table. The diathermy electrode is shown wrapped round one leg.

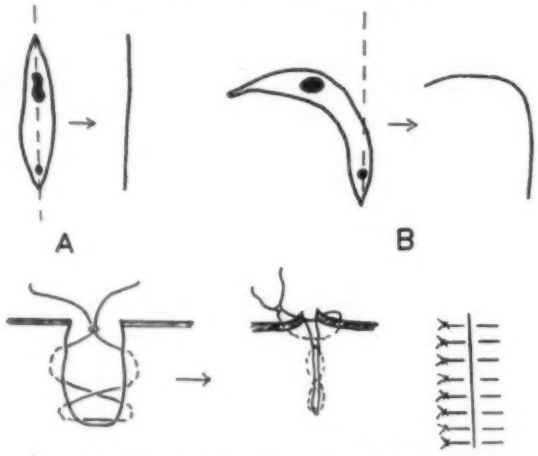

FIG. 3.—An elliptical incision (A) in the long axis of the body is usual. A curved boomerang rotation flap incision (B) is needed when secondary openings are sited well away from the midline. The placing of the buried figure-of-8 catgut stitch is shown whereby the deep fascial layers are united and tension on the skin edges is avoided. Interrupted vertical mattress sutures achieve neat eversion of the skin edges.

Haemostasis is secured with diathermy or with fine plain catgut, and the subcutaneous and deep fascial layers are mobilized to permit suture. I do not favour deep tension sutures, and all strain on the wound is taken up by a row of buried figure-of-eight catgut sutures (Fig. 3), taking care that the deep fascial layer is included. All these sutures are placed in position but not tied until the plaster strips holding the buttocks apart are cut. In this way the wound comes together so that vertical mattress sutures may be placed in the skin to cause eversion of the wound edges without any tension. Dressings are not sewn on, for such a method causes discomfort to the patient and constant movement of a wound which should be left at rest. Instead, the wound is sprayed with "nobecutane," and this is allowed to dry before a gauze dressing is applied with supporting wool and strapping. The wound is sealed from the anus by the careful application of waterproof strapping: this is important, because some sinuses encroach on the anal canal.

The patient is nursed in the prone position, but is got up after two days, being encouraged to stand rather than sit unless it be on a "commode" type of seat. Theatre dressings are untouched as long as possible (five to seven days), and then, depending on its condition, the wound is cleaned with ether and powdered with thymol iodide ("aristol") twice daily or dressed with a spirit roll. It may be necessary to cut any short hairs that are regrowing close to the edges of the incision.

A low-residue diet is continued for five days. Enemata are given on alternate days after this. Baths are given after seven days. Alternate sutures are removed on the eighth day, the remainder being left until the tenth or twelfth day.

Summary

Most cases of pilonidal sinus can be treated by excision and primary closure of the wound in preference to excision and allowing the wound to granulate—a method still commonly taught and practised. With primary closure the recovery time is shortened, and the risk of recurrence is no greater than that following the other method. The experience of primary closure in 112 cases is recorded and a technique is described.

My grateful thanks are due to Sister M. Simpson for the development of the nursing regime described above.

SENSITIVITY TO PHENINDIONE

REPORT OF A CASE OF SEVERE DIARRHOEA

BY

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The cases of severe sensitivity to phenindione described in the literature were found by Burns and Desmond (1958) to be manifested by pyrexia and blood dyscrasia, less commonly by a rash, and in two cases by jaundice. Apparently no case of severe diarrhoea produced by phenindione (" dindevan ") has been described.

Case Report

The patient, a 67-year-old retired consultant physician, had always enjoyed perfect health up till 1951, and, in particular, had an uneventful gastro-intestinal history apart from appendicectomy at the age of 28. He had had his bowels open twice a day for as long as he could remember, and the motions had always been normal.

In 1951 he had a small posterior myocardial infarction. He was initially treated with bed rest only, but when in the fourth week a phlebitis in the right leg was followed by a massive pulmonary infarct of the right lung, ethyl biscoumacetate (" tromexan ") was used as an anticoagulant. The anticoagulant therapy was continued for three months. During this illness he was troubled by severe constipation, which required several enemata a day for relief. In 1954 he was found to have a popliteal aneurysm in the right leg, for which a lumbar sympathectomy was performed. For some weeks after the operation he was again treated with ethyl biscoumacetate, which produced no certain side-effects.

Since that time, up till November, 1958, he was able to lead an active professional life. He had occasional intermittent claudication in the right leg, which became more and more troublesome during the course of 1958. His bowels had, if anything, been slightly constipated and he occasionally used a little " agarol."

Early in November, 1958, whilst gardening, he injured the big toe of his right foot ; this was followed by spreading superficial venous thrombosis. At this stage it was obvious that the aneurysm of the right popliteal artery had thrombosed and that the arterial blood supply to the right foot was extremely precarious. It was also discovered that there now was an aneurysm of the left popliteal artery. He was admitted for observation to the Radcliffe Infirmary under the care of Professor P. R. Allison and Professor Sir George Pickering.

Anticoagulants were started on November 9. This time phenindione was used. Conservative treatment made little difference to the condition of the leg, and an above-knee amputation was undertaken on November 26. Before and during the immediate post-operative period, large doses of analgesics (heroin and pethidine) and of hypnotics (barbiturates) were required to allay pain and ensure sleep. If anything, he was constipated. Throughout he had been on phenindione, and the one-stage (Quick) " prothrombin time " was kept within a range of 10–20%. From about December 20—that is, about six weeks after phenindione was first used—he noticed that his stools were getting soft and bitty. He put this down to the large quantities of fruit he had been eating during his convalescence. The healing of the stump proceeded uneventfully. In view of his history and the left popliteal aneurysm, it was decided to keep him on anticoagulants for an indefinite period. He was discharged from hospital on January 9, 1959.

Shortly after his return home he developed frank diarrhoea. He initially had four to five actions a day, but the condition steadily deteriorated, and by January 25 he had developed a frank steatorrhoea, with watery white stools. At that stage he was only having barbiturate (" tuinal ") at night and phenindione in a dose sufficient to keep the prothrombin level within the therapeutic range (10–20%). The dose of phenindione varied, but was usually of the order of 50 mg. a day. Codeine phosphate, a kaolin and morphine mixture, and a low-fat diet made no difference to the condition. Phenindione seemed to be the only drug that could be responsible for the diarrhoea, and he was switched to ethyl biscoumacetate, which he had previously tolerated. Dr. John Badenoch saw the patient and agreed that clinically he appeared to have steatorrhoea.

A barium enema examination showed a few diverticula of the sigmoid colon only, and a barium-meal and follow-through examination revealed no abnormality other than intestinal hurry. Hb was 105%, W.B.C. 10,500 ; the film showed a neutrophil leucocytosis, and the E.S.R. was 8 mm./hour. Plasma proteins were 6.9 g. per 100 ml. (albumin 3.7 g.). Flocculation tests were negative. Bilirubin was 0.4 mg. per 100 ml. There were traces of occult blood in the stools, but no pathogens were isolated. A 24-hour stool specimen obtained on January 28 contained 39.5 g. of fat and 3.5 g. of nitrogen. The patient was put on a convalescent sprue diet and given folic acid, " multivite," vitamins A and D, calcium gluconate, and vitamin B_{12}. Before this treatment was started—that is, three to four days after he was switched from phenindione to ethyl biscoumacetate—his general condition improved, and within a week his stools became normal, with a return of his former bowel habits. On February 1 a 24-hour specimen of stool showed a content of only 10.8 g. of fat and 1 g. of nitrogen.

Although phenindione was thus suspect, it was thought unlikely that it had been responsible for the diarrhoea, and for convenience the patient was again switched to phenindione on February 11. He continued on a convalescent sprue diet with vitamin supplements as outlined above. On February 12 his motions became loose, and by the 16th they had become very loose and fluid. He had his bowels open six or seven times in the course of the day and night. The motions were now more like dysentery stools, watery, with blood and mucus. Codeine phosphate made little difference. The stools again yielded no pathogens. The blood electrolytes remained normal, and the blood picture was normal. On February 16 it was decided to discontinue all medication except the anticoagulant therapy and to revert to ethyl biscoumacetate. In spite of the exhausting diarrhoea, the patient felt hungry ; he found his sprue diet quite insufficient, and was allowed a normal diet, avoiding excess fat. Within a week his stools again improved. The motions became normal and he was eating with normal appetite, and was apparently perfectly well by February 26. He has since been on ethyl biscoumacetate, which has presented no problems.

Discussion

In this patient the onset of diarrhoea occurred about six weeks after phenindione therapy had been started. By about the eleventh week he developed a frank steatorrhoea. When the phenindione was discontinued and ethyl biscoumacetate substituted, the condition improved after four to five days. At first he

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received in addition a sprue diet and additional vitamins. When ethyl biscoumacetate was discontinued and phenindione substituted, the diarrhoea returned within a few days, this time as a bloody dysentery (possibly because the patient was now having a sprue diet). When the anticoagulant was changed back to ethyl biscoumacetate the condition improved after four to five days, although the sprue regime was abandoned. No clinical or laboratory findings to suggest any other cause for the diarrhoea were elicited. At no stage was there any fever, blood dyscrasia, or jaundice. The liver-function tests were not grossly deranged, although the plasma albumin (3.7 g. per 100 ml.) was a trifle low. Burns and Desmond (1958), summarizing the day of first appearance of other observed sensitivity reactions to phenindione, found that these occurred at a variable time, from 2 to 38 days after administration had begun. In the present case six weeks elapsed before the onset of any certain symptom.

Summary

A severe drug-sensitivity reaction manifesting itself by frank steatorrhoea developed in the seventh week of phenindione administration to a 67-year-old male patient suffering from peripheral vascular disease. The steatorrhoea cleared after ethyl biscoumacetate was substituted. On recommencing phenindione the diarrhoea returned, this time as a bloody dysentery, only to disappear again when ethyl biscoumacetate was substituted.

My thanks are due to Dr. John Badenoch for his help in the investigation of this unusual problem, to Dr. R. Biggs, Dr. R. G. Macfarlane, Professor P. R. Allison, and Professor Sir George Pickering for their valuable suggestions.

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WHOOPING-COUGH IMMUNIZATION

CLINICAL FOLLOW-UP OF FIRST BARKING FIELD TRIAL, 1955

BY

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AND

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In our original work (Spiller *et al.*, 1955) we stated that we were following up clinically the immunized children and that we would give the results at a later date.

Two groups of children were immunized against diphtheria and whooping-cough, the one group by the combined method—that is, three injections of 1 ml. of diphtheria-pertussis prophylactic W.D.P. (red) Wright-Fleming, at monthly intervals; the other by the separate method—that is, three injections of 1 ml. of suspended whooping-cough vaccine (Glaxo), followed by two injections of 0.5 ml. P.T.A.P. The first injections were given between the ages of 2 and 5 months inclusive, and blood samples were taken at the age of 15 months in the case of 160 of these children so as to assess their antibody level. This was the original work on which we reported, and, furthermore, 52 of these children have recently been bled again, 4–4½ years after the end of primary immunization in infancy. The main object of these long-deferred bleedings was to determine the diphtheria antitoxin titres at pre-school entry age.

The Investigation

A careful clinical follow-up has been carried out on the whole 714 children who were originally incorporated in the research, so as to ascertain the number of those who did actually develop whooping-cough during the years that have followed. It may be interesting to mention here that over 300 of the children changed addresses at least once or twice during the course of the follow-up, and it required the assistance of rent offices, electoral registers, as well as health visitors, relatives, and neighbours in tracing them, as the families rarely notified a change of address. Because the blood results (agglutination titres) appeared to indicate an eminently satisfactory protection level, it may be thought that the clinical result is disappointing. It should be remembered, however, that we have not merely relied on whooping-cough notifications but have followed up individually each case by careful questioning. Many cases of doubtful cough that were not notified were accepted as whooping-cough because of various factors—for example, other simultaneous cases of suspicious cough in the family; an unusually prolonged and violent cough with no other obvious cause, and no previous history; other whooping-cough contacts, etc.

Whooping-cough Incidence. — Of the original 714 children incorporated in the scheme, 64 either lapsed in their attendance for injections or left the country and could not be followed up. Of the remaining 650 (315 in the "separate" group and 335 in the "combined") it appears that 22 almost certainly had whooping-cough, mostly in a mild form (but some were severe); and 11 were reported as doubtful cases, and *may* have had it very mildly. This gives a maximum frequency of 5.07% or a minimum of 3.38%, *over a total period of three years.*

Separate Versus Combined Injections.—Of the 22 confirmed cases, 8 had separate injections and 14 had combined injections. Of the 11 doubtful cases, 4 had separate injections and 7 had combined injections. Although it seems at first that the separate method of injection gives better protection, analysis of the figures gives $\chi^2=2.1$, $P=0.1$, indicating no significant difference.

Severe Attacks Analysed.—There were 4 children who had severe attacks, and 3 of these were immunized by the combined method; 2 of them had nearly a three-months gap between two of their whooping-cough injections and developed the disease respectively five months and one year after the last injection. The other 2 children developed whooping-cough 35 and 30 months after the last injection, so that one can assume that they were losing their artificial immunity.

Gaps.—Of the remaining 18 confirmed cases, 6 had gaps of two to three months during the course of their injections; the other 12 appeared to have attended at regular monthly intervals for injections. In the doubtful group all 11 children had attended for injections at monthly intervals—that is, there were no gaps. If we take the 33 children who had (or may have had) whooping-cough and assess the number of "gaps" of two to three months and over in their attendance we find there were eight gaps—that is, 24%. In the 617 remaining children there were attendance "gaps" in 9.7%. This difference does seem somewhat significant.

It should perhaps be explained that many of the " gaps " were due to interruption of immunization during a polio season.

Injection–Disease Time Lapse.—The lapse of time between the date of last whooping-cough injection and the development of whooping-cough was 1.7 years in the doubtful group and 1.6 years in the confirmed group. Actually the shortest time lapse in these cases was four months and the longest 35 months.

Age at First Injection.—The average age of the affected children at their first injection was 3.7 months in both the confirmed and the doubtful group, whereas the average age for the whole group was 3.9 months.

Blood Results.—Only 10 of the 33 children who developed whooping-cough had been bled at the age of 15 months and had had their pertussis agglutination titres measured. These varied from 1/20 to 1/1,280, from which it may be concluded that agglutination titre is no reliable index of protection against whooping-cough. This agrees with the findings of Horton and Standfast (1953).

Home Contacts.—In our follow-up questioning the parents of 35 infants reported that their child had been a home-contact with another suffering from whooping-cough; none of these 35 developed the disease. Unfortunately we have no information on the home-contact rate in respect of the 22 almost certain cases and 11 doubtful ones, although, of course, as they developed the disease they must have been in contact somewhere with an infected child.

Notification Rate.—Of the 22 definite cases, only 5 were notified in our area. Another 7 may have been notified out of the area, but this still leaves 10 definite cases not notified in their own area. One should be wary, therefore, of accepting notification incidence as a reliable measure of whooping-cough prevalence.

Summary

Two groups of infants were inoculated against diphtheria and pertussis in early infancy. One group received three doses of whooping-cough vaccine at monthly intervals, followed by two doses of P.T.A.P. The other group received three doses of combined formol-toxoid and whooping-cough vaccine. In the subsequent three years no significant difference was found in the frequency of undoubted whooping-cough in the two groups. Since, however, 22 children did develop the disease some 19 months after the end of primary immunization, a booster dose at the age of 15–18 months seems to be recommended. As whooping-cough is a more serious disease in very young babies, it might be thought advisable to give the first injection at 2 months or even younger in view of the fact that those immunized at 2 months appeared to be as well protected as those whose first injections were given at 3, 4, or 5 months.

Thanks must be accorded to Dr. G. Stewart, County Medical Officer, Essex, and to Dr. F. Groarke, Area Medical Officer, Barking, for permission to carry out the work. We gratefully acknowledge the assistance of colleagues, especially the invaluable help of Mr. Brian in the collection of blood samples, and of Mrs. Pratt, the nurse who assisted at these sessions. Thanks are also due to Mrs. Tidbury and Miss Valerie Harper for many hours of cheerful and willing clerical assistance.

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Medical Memoranda

Ehlers-Danlos Syndrome with Congenital Herniae and Pigeon Breast

The Ehlers–Danlos syndrome, described by Ehlers in 1900 and by Danlos in 1908, is rare. The classical features are: (1) hyperelasticity of skin; (2) friability of the skin and the blood vessels, with a tendency for wounds to gape and a susceptibility to intracutaneous or subcutaneous haemorrhages, even from trivial trauma, or occasionally to visceral haemorrhages; (3) profuse scarring, usually papyraceous in type; (4) hyperextensibility of joints; (5) frequent presence of tiny mobile subcutaneous nodules, probably of a lipomatous nature; and (6) familial incidence of one or more of the above features.

CASE REPORT

A 3-year-old French Canadian boy was admitted to Ottawa General Hospital on July 6, 1957, because of a lacerated injury over the right knee. Even minor injuries were apt to cause skin cuts, lacerations, bruises, and bumps, and he had numerous scars over his body. Since birth his skin had been very soft and elastic. He was born prematurely and had congenital umbilical and inguinal herniae. The umbilical hernia was repaired. At the age of 1 year he received multiple lacerated injuries in a car accident; the wounds gaped after the removal of only two stitches on the fifth day. His father's skin was soft, doughy, and slightly hyperelastic; his palms and soles were soft, his fingers could be slightly overextended, and his feet were flat. He had no scars or friability of skin. No abnormalities were found in other members of the family.

On physical examination the boy, though mentally alert, was seen to be somewhat underdeveloped, being 2 ft. 10 in. (86 cm.) in height, and weighing 27 lb. (12.2 kg.). His head circumference was 20 in. (51 cm.) and the fontanelles were closed. He could stand and walk normally. He had a pigeon breast (Fig. 1), and there were numerous scars all over his body, mostly on the face, head, left arm, knees, legs, and feet. Some of the scars appeared to be due to stitched or unstitched wounds. A few scars were papery, particularly over the lower abdomen and the forearms. There were a few bruises. A fresh lacerated gaping wound was seen across the front of the right knee.

The skin was doughy, soft, velvety, and elastic, and could be easily stretched for about 1 to 2½ in (2.5 to 6.4 cm.) over the arms, forearms (Fig. 2), thighs, and legs. When let go the skin immediately returned to its position, like a piece of soft rubber, leaving no wrinkles or folds. No subcutaneous nodules were palpable. The mucus membrane was not elastic.

The child had large bilateral, reducible, indirect inguinal herniae, and the scar of the repaired umbilical hernia was visible.

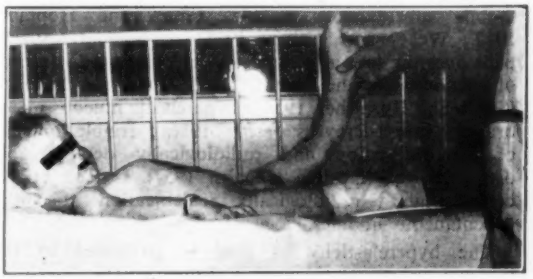

FIG. 1.—Hyperextensible knee and pigeon breast.

The limbs were hypotonic. The fingers (Fig. 3) and toes could be easily overextended by 180 degrees or twisted without any discomfort or pain. The knees (Fig. 1), elbows, wrists, and ankles could also be overextended. Abnormal lateral movements were possible at the knees. Both feet were flat.

Urinalysis, leucocyte, erythrocyte, and platelet counts, bleeding and clotting times, and haemoglobin were normal. Rumpel–Leede sign was negative.

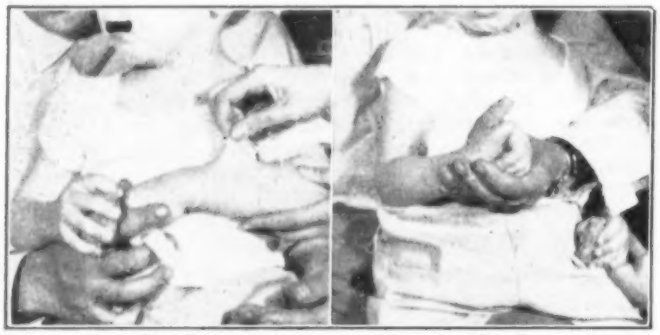

FIG. 2 FIG. 3

FIG. 2.—Hyperelastic skin of the forearm. FIG. 3.—Extremely hyperextensible fingers.

Skin Biopsy.—Skin obtained from above the patient's right knee was compared with a few control sections of skin obtained at necropsies from patients of about the same age and nutritional state. Histological examination showed an increase in the amount of elastic tissue and a considerable deficiency of collagenous connective tissue of the corium. The epidermis was wrinkled.

COMMENT

This case illustrates the chief features of Ehlers–Danlos syndrome. Two associated defects, which apparently have not been previously reported, were pigeon breast and congenital umbilical and inguinal herniae. The skin biopsy showed the usual picture described as typical of this syndrome.

The elasticity of the skin in these cases is sometimes remarkable. Murray and Tyars (1940) reported a case where it was possible to pull the skin from the sternal region to cover the mouth. The wounds to which the skin is very prone usually leave papyraceous scars which may be very profuse. The joints are lax and hyperextensible. The fingers and toes may show double-jointedness. The joint instability can cause subluxations, dislocations, sprains, and a tendency to fall on walking which may lead to repeated fractures, as observed by Johnson and Falls (1949).

Many other abnormalities have been reported in association with this syndrome, including lenticular opacities (Johnson and Falls, 1949); molluscoid and raisin-like tumours (Ronchese, 1936); hard, freely mobile subcutaneous nodules (Shaw and Hopkins, 1912; Weber and Aitken, 1938); redundant knuckle pads over the toes and tumour-like formations at points of friction (Ross and Dooneief, 1957); pectus excavatum (Smith and Hornisher, 1954); hyperelastic mucous membrane (Gilbert-Dreyfus *et al.*, 1936); friable mucosa of sigmoid colon and radiologically demonstrable diverticula of intestine (Jacobs, 1957). Holt (1946) demonstrated radiologically calcification of the subcutaneous nodules.

The hyperelasticity of skin is attributed to the increase in elastic tissue and decrease in collagen of corium. The blood vessels, although very friable, are usually unremarkable on histological examination.

The cause of this syndrome is not understood. Some relate it to possible endocrine imbalance, neurofibromatosis, abnormalities of calcium or carbohydrate metabolism, and often prematurity. The syndrome is often familial and is inherited as an incomplete dominant. Coe and Silvers (1940) reported affection of four generations. Johnson and Falls (1949), in a comprehensive study, reported a family pedigree covering six generations, with 21 men and 11 women affected.

It has been suggested by Benjamin and Weiner (1943) and others that some disturbance in the embryonic mesenchyme may be responsible for the anomalies of the skin, which is of ectodermal origin, and of the capsules and ligaments of the joints, which are of mesodermal origin. A further study of the internal organs and, wherever possible, necropsy examination might reveal evidence of mesenchymal dysplasia in other organs such as dissecting aneurysm of the aorta and other blood vessels and congenital anomalies of the urinary tract as have been reported with Marfan's syndrome. Congenital lenticular defects, also associated with Marfan's syndrome, have been reported in cases of Ehlers–Danlos syndrome.

I thank Dr. J. S. Campbell, Associate Professor of Pathology, for examining the skin biopsies; Dr. D. J. Conway, Professor of Paediatrics, University of Ottawa, for his help; Dr. W. A. Walker, for the photograph shown in Fig. 1; and Miss M. Gauthier for secretarial assistance.

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Vaccination against yellow fever, which is necessary for those intending to visit a number of Central and South American and mid-African countries, is likely to be made more easily obtainable. Up to the present such vaccination has only been available at Regional Blood Transfusion Centres and certain hospital laboratories with special storage facilities and knowledge of necessary laboratory technique. Now that the vaccine is prepared in dried form and may be stored in an ordinary domestic refrigerator, local health authorities have been asked by the Ministry of Health to offer yellow fever vaccination to those requiring it. The number of centres where it can be obtained will thus be increased if the local authorities are willing to provide the service (Ministry of Health, No. 10, June 6).

Reviews

PHYSIC AND METAPHYSIC

Revolution in Medicine. Why Patients Need It and How Doctors Could Bring It About. By Brian Inglis. (Pp. 279. 21s.) London: Hutchinson. 1958.

Ever since general medicine adopted more empirical and mechanistic methods of treatment, instead of those based on such things as the supposed part played by metaphysical humours, vapours, innate heats, and the like, in the causation of bodily illness, the efficiency of therapeutic methods has forged ahead by stupendous leaps and bounds. Yet some doctors and laymen alike are far from satisfied with these truly tremendous advances. They still wish for systems of treatment in which philosophical theories and concepts again play a larger part, and where as much or even more attention is paid to the psychological and spiritual than to the material in treatment.

Brian Inglis, of the *Spectator*, has written a book which is very critical indeed of the present-day practice of medicine and its materialistic viewpoints. Inglis's particular preoccupation is the part that psychological and other stresses may play in bodily disease processes, and the way this possibility is being ignored at the present time in treatment. He would have us consider whether cancer, tuberculosis, many skin diseases, digestive upsets, diabetes, and the like are not wholly or in part stress disorders, and he feels that medicine should be prepared to give many more sufferers from some of these diseases appropriate forms of psychotherapy. As the blurb to this book puts it: "The emphasis is now on physical cures, but the majority of patients are suffering from diseases which require a very different approach." This book is a veritable layman's guide to psychosomatic medical theorizing and practice. The viewpoints and writings of the various schools of psychosomatic and psycho-analytically orientated psychiatrists are abstracted and expounded. But it is a piece of special pleading, and often the information conveyed by the particular selection of sources quoted can be misleading.

Inglis and other psychosomatic proponents should be constantly reminded of the fact that medicine has actually proved to be at its most effective just when it has deliberately been able to bypass stress as the special component to be treated in bodily and mental diseases. For instance, despite the part obviously played by stresses of various kinds in bringing on attacks of tuberculosis, this killing disease has been dealt with far more effectively with the discovery of I.N.A. and P.A.S. These drugs kill the bacilli and so enable the individual to tolerate again all the necessary stresses of living. Previously, when only rest and environmental and psychological adjustments could be used to help these patients, they literally died in their thousands each year. Inglis should also remember that epileptics can now mostly tolerate any amount of stress once the appropriate modern biochemical anticonvulsants have been found which suit them. And tranquillizers and sedatives usually help far more neurotic and psychosomatic patients in actual medical practice than does any amount of psychological therapy and talk.

In this book Brian Inglis constantly criticizes medicine for its present preoccupation with physical treatment. But I am sure he would be a very unhappy man indeed if he did actually find himself back in an eighteenth-century metaphysically orientated medicine, and if he found that he was being recommended only psychotherapy or exorcism for his toothache or his tuberculosis. And even in psychological medicine, it has only been with the advent of the new empirical and mechanistic physical treatments, after thousands of years of religion, psychotherapy, and verbal exorcism of all types and kinds, that it is at last becoming possible to start to think about emptying our mental hospitals, and really to provide some effective relief for the intolerable suffering of so many of the mentally ill.

Inglis is right to remind us that psychotherapy is always a valuable part of all medical treatments and should not be neglected. But it really cannot be expected to move mountains. And unfortunately, miracles excepted, it has too often proved a remarkably limited therapeutic weapon throughout the ages when used alone in the treatment of the serious physical or mental illnesses.

WILLIAM SARGANT.

REHABILITATION OF THE HAND

Rehabilitation of the Hand. By C. B. Wynn Parry, M.B.E., M.A., D.Phys.Med., N. R. Smythe, M.A.O.T., and L. E. Baker, M.C.S.P. (Pp. 273+vii+17; illustrated. 45s.) London: Butterworth and Co. (Publishers) Ltd. 1958.

The hand is of such great importance to the human economy that it is not surprising to find several books devoted entirely to its diseases and especially to the surgical treatment of its injuries and deformities. In their preface to *Rehabilitation of the Hand* the authors draw attention to the fact that "none of these books to our knowledge has concerned itself with detailed conservative treatment or the niceties of after care." The present volume therefore is to be welcomed as a guide to the practitioner and surgeon on what can be accomplished by rehabilitation of the hand after treatment of the active stage of any disability is completed. The various methods described are those employed in the Medical Services of the Royal Air Force.

The book is well produced with an abundance of excellent illustrations, the serial photographs showing the progress of cases under treatment being particularly valuable. The modern use of electrodiagnostic methods, such as strength-duration curves and electromyography, is very clearly and adequately dealt with. A final chapter on "National Facilities" gives a useful and informative account of the disposal of the disabled to resettlement schemes, Government training centres, sheltered workshops, and so on, together with the complicated question of compensation.

There are very few misprints, but the caption to Fig. 76, where "flexor" instead of "extensor" appears, could be misleading. In the account of the mechanism by which abduction of the arm is brought about when the deltoid is paralysed it seems doubtful if the long head of the triceps could be effective, except for its use as a stabilizer of the joint. Altogether a book which deserved to be written.

NORMAN C. LAKE.

MEDICAL IDEAS

Centaur. Essays on the History of Medical Ideas. By Félix Martí-Ibáñez, M.D. (Pp. 714+xvii. $6.00.) New York: MD Publications, Inc. 1959.

Dr. Martí-Ibáñez, Spanish physician and medical historian, professor and director of the history of medicine, New York Medical College, in this bulky

volume surveys mankind from China to Peru. Wit, learning, and wide reading in Spanish, English, French, German, and Italian literature go to the making of the book, which, as the author states, "presents a theme in short, vivid flashes that incite the desire to know more about it, to seek out more erudite treatises on the subject." Thus the book is a collection of brief sketches of medical history, including also excursions into art, philosophy, sociology, and psychology.

Sherlock Holmes told Watson that excellence at chess was one mark of a scheming mind. Dr. Martí-Ibáñez has plumbed even deeper. His essay on the psychology of chess can be read as an amusing satire on Freud, but his other psychiatric essays show that he is an enthusiastic Freudian and really supposes chess to be full of more involved complexes and symbols than gambits. The essays on Ramón y Cajal and Ehrlich are good, and the excellent appreciation of Sigerist is that of a grateful friend as well as of a brother historian. Although imagination sometimes runs away with accuracy, all the essays are worth reading. The title of this book is taken from the centaur Chiron, who taught Aesculapius art and medicine: it is one of a tetralogy, so that we may expect three further volumes.

ARTHUR S. MACNALTY.

NOT SO SIMPLE

Akute Innere Krankheiten. Diagnostische und Therapeutische Hinweise in Tabellarischer Übersicht. By H. A. Kühn, H. Klepzig, and E. Schildge. Foreword by Prof. Dr. Ludwig Heilmeyer. Second edition. (Pp. 247+vi. DM. 16.50.) Stuttgart: Georg Thieme Verlag. 1959.

To those who like their diagnosis and treatment served in tabular form this book on acute medical diseases should be palatable. The basic purpose is to define problems of diagnosis and prescribe tersely their treatment. The book is meant to help the physician in medical emergencies. In fairness to the authors, it must be said that they are aware of the difficulties presented by tabular medicine of this kind and recognize that it cannot take the place of a treatise in medicine. It is really meant for quick orientation and use in emergencies. On the other hand such a ready reckoner suggests that the doctor is a clerk or a machine and cannot help to raise the standard of clinical medicine. Acute medical emergencies are dealt with, in the main, according to the various systems. In relation to the cardiovascular system, cardiac pain, palpitation, tachycardia, bradycardia, circulatory collapse, are listed; and under the respiratory system acute breathlessness, pain on breathing, cough, and blood-streaked sputum come into the filing list and are dealt with as exhaustively as the nature of the book permits.

The first chapter deals with the differential diagnosis of coma, acute fevers of every description, acute general cyanosis, jaundice, acute oedema, and the anaemias.

The final chapter tabulates the important drugs available for the treatment of each disease and in most cases the appropriate dosage. So simple does it appear that one would dread the book falling into the hands of the uninitiated, who might be led to believe that here they held the key to medical practice. The student, cramming for his final examination, might refer to it the night before. Wisely used, it probably serves a purpose, but one must lament the confusion it exhibits as between facts and knowledge.

PHILIP ELLMAN.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

The Degenerative Back and Its Differential Diagnosis. By P. R. M. J. Hanraets, M.D. (Pp. 690; illustrated. £5 5s.) London, Amsterdam: Elsevier Publishing Company. 1959.

A Synopsis of Obstetrics and Gynaecology. By Aleck W. Bourne, M.A., M.B., B.Ch.(Camb.), F.R.C.S.(Eng.), F.R.C.O.G. Twelfth edition. (Pp. 632+vii; illustrated. 35s.) Bristol: John Wright and Sons Ltd. 1959.

Comparative Anatomy. By William Montagna. (Pp. 397+x; illustrated. 48s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall, Limited. 1959.

Angiocardiopneumographie Élargie. Méthode d'Opacification Vasculaire Générale par Voie Veineuse. By P. Viallet, L. Sendra, L. Chevrot, P. Aubry, and P. Combe. (Pp. 107; illustrated. 4,400 fr.) Paris: Masson et Cie. 1959.

Healthier Babies—Happier Parents. A Practical and Reassuring Handbook for Parents. By Henry K. Silver, M.D., C. Henry Kempe, M.D., and Ruth S. Kempe, M.D. With a foreword by Philip Evans, M.D., M.Sc., F.R.C.P. (Pp. 256; illustrated. 8s. 6d.) London, Glasgow: Collins. 1959.

The Dentition of the Growing Child. A Longitudinal Study of Dental Development between 3 and 18 Years of Age. By Coenraad F. A. Moorrees. (Pp. 245+vi; illustrated. 45s.) Cambridge, Massachusetts: Harvard University Press. London: Oxford University Press. 1959.

Tumeurs Bénignes des Os et Dystrophies Pseudo-tumorales. By André Trifaud, Henri Bureau, with the collaboration of Henri Payan. (Pp. 279+vi; illustrated. 4,200 fr.) Paris: Masson et Cie. 1959.

Allergie und Allergische Erkrankungen. Vol. 1. ***Allgemeiner Teil.*** Edited by E. Rajka. (Pp. 638; illustrated.) Budapest: Akademiai Kiado. 1959.

An Introduction to Surgery for Dental Students. By R. P. Jepson, F.R.C.S., and B. N. Catchpole, F.R.C.S. (Pp. 166+x; illustrated. 21s.) London: English Universities Press Ltd. 1959.

Sympathectomy. An Anatomical and Physiological Study with Clinical Applications. By P. A. G. Monro, M.A., M.D. (Cantab.), M.Sc.(London). With a foreword by J. D. Boyd, M.A., M.D., M.Sc. (Pp. 290+xx. 75s.) London: Oxford University Press. 1959.

Die Mitogenetische Strahlung. Ihre Physikalisch-chemischen Grundlagen und ihre Anwendung in Biologie und Medizin. By A. G. Gurwitsch and L. D. Gurwitsch. (Pp. 308; illustrated. DM. 27.65.) Jena: VEB Gustav Fischer Verlag. 1959.

Cellular and Humoral Aspects of the Hypersensitive States. A Symposium held at the New York Academy of Medicine. Edited by H. Sherwood Lawrence, M.D. (Pp. 667+xii; illustrated. £6 10s.) London: Cassell. 1959.

Nierenkrankheiten. Physiologie, Pathophysiologie, Untersuchungsmethoden, Klinik und Therapie. By Hans Sarre. Second edition. (Pp. 555+xxiii; illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1959.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., and Robert F. Loeb, M.D., Sc.D., D.Hon.Causa, LL.D. (Pp. 1,665+xxxiii+lxxxix; illustrated. £5 15s. 6d.) Philadelphia, London: W. B. Saunders Company. 1959.

Abhandlungen über die Pathophysiologie der Regulationen. Vol. 2. ***Antibiotika und Neurohumorale Regulationen.*** By Ladislaus Mosonyi, M.D. (Pp. 60; illustrated. DM. 7.10.) Jena: VEB Gustav Fischer Verlag. 1959.

Klinik und Therapie Symptomatischer Anfallsleiden. By Dr. K. Nittner and Dr. W. Steinmann. ***EEG und Hirntrauma.*** By Dr. H. W. Steinmann. With a foreword by Professor Dr. W. Tönnis. (Pp. 175+viii; illustrated. DM. 36.80.) Stuttgart: Georg Thieme Verlag. 1959.

Der Gesundheitszustand der Heimkehrer. Ergebnisse von Forschungsaufträgen des Bundesministeriums für Arbeit und Sozialordnung. (Pp. 91. DM. 12.80.) Stuttgart: Georg Thieme Verlag. 1959.

Asexualization. A Follow-up Study of 244 Cases. By Johan Bremer. (Pp. 366. 35s.) New York, London: The Macmillan Company. 1959.

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LONDON
SATURDAY AUGUST 15 1959

OUR PATRON THE QUEEN

Members of the B.M.A. will welcome with especial pleasure the news that the Queen is expecting another child. Her Majesty is our Patron, and her husband, Prince Philip, our President-Elect. For them, as it is for us, it is good to know that the Queen will be safely cared for in the coming months by medical men of the highest professional repute and skill.

BACK TO NORMAL

The printing dispute is over. During the past seven weeks the *British Medical Journal* has been produced in peculiar circumstances. Some of the difficulties we have had to contend with were described in last week's issue. We apologize to readers for printing errors and for other imperfections. It is deeply to be regretted that the dispute has gravely delayed the appearance of articles already accepted for publication, and that there has been delay in communicating with authors. It will be some time before we shall be able to catch up with arrears of work and publication. We would beg readers' tolerance in the meanwhile.

AN ARTIFICIAL LIVER?

High levels of ammonium in the blood are often found in patients in hepatic coma.[1-3] Moreover, the administration of ammonium salts[4,5] may precipitate coma in some patients with liver disease. This has led to the idea that ammonium intoxication may sometimes cause hepatic coma. Consequently, treatment has been directed towards reducing the ammonium level in the blood.

Glutamic acid has been given because it combines with ammonium to form innocuous glutamine,[6] and arginine has been tried since it is said to stimulate the Krebs cycle in the liver and so lead to the detoxification of ammonium as urea.[7] Both measures sometimes reduce ammonium levels in the blood, but they have not been consistently successful,[8-10] and neither looks like holding its place in routine clinical practice.

In 1956 J. E. Kiley and his co-workers[11] in Albany, New York, used an artificial kidney of the Kolff type to reduce blood ammonium. A single passage through the artificial kidney extracted 50% of ammonium. These authors now report the further application of the method.[12] All five patients treated were suffering from liver disease, and all were in coma, with high ammonium levels in the blood. In three patients with portal cirrhosis the coma had been precipitated by haemorrhage from oesophageal varices, and in two of these the haemodialysis resulted in a fall of the ammonium levels, with return of consciousness. In the third the haemodialysis was limited by clot formation and the ammonium level did not fall; this patient died two days later. These three patients did not have any other biochemical abnormalities. Two other patients in hepatic coma, but without any precipitating gastro-oesophageal haemorrhage, were treated. These had other severe biochemical abnormalities—one uraemia and the other hypokalaemia, hypochloraemia, and alkalosis. In both haemodialysis resulted in removal of large amounts of ammonium nitrogen and other non-protein nitrogenous constituents of the blood. One patient improved temporarily, but both died within two days. The authors conclude that dialysis is of no value when damage to the liver is far advanced and the ammonium level rises, though there is no precipitating factor, and dietary intake of protein is low. The only indication for dialysis is when haemorrhage into the intestines is so massive that the load of ammonium from the blood would be overwhelming in spite of therapeutic measures such as withdrawal of protein from the diet and administration of wide-spectrum antibiotics; another indication would be associated uraemia. But it is worth bearing in mind that other treatment such as the administration of corticosteroids and glutamate was sometimes being given at about the same time as the dialysis.

A simpler technique is described by D. C. Schechter and colleagues[13] from the Jefferson Medical Center in Philadelphia. The blood is simply passed through an ion-exchange resin. The one used sequesters ions such as calcium, magnesium,

[1] Kirk, E., *Acta med. scand.*, 1936, Suppl. **77**, 1.
[2] Traeger, H. S., Gabuzda, G. J., Ballou, A. N., and Davidson, C. S., *Metabolism*, 1954, **3**, 99.
[3] Phear, E. A., Sherlock, S., and Summerskill, W. H. J., *Lancet*, 1955, **1**, 836.
[4] van Caulaert, C., Deviller, C., and Halff, M., *C.R. Soc. Biol. (Paris)*, 1932, **111**, 739.
[5] Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S., *New Engl. J. Med.*, 1952, **247**, 239.
[6] Walshe, J. M., *Lancet*, 1953, **1**, 1075.
[7] Najarian, J. S., and Harper, H. A., *Amer. J. Med.*, 1956, **21**, 832.
[8] Alexander, R. W., Berman, E., and Balfour, D. C., Jr., *Gastroenterology*, 1955, **29**, 711.
[9] Schwartz, I. R., Lehman, E., Hammond, J., Seibel, J. M., and Goldson, F., ibid., 1956, **30**, 869.
[10] Reynolds, T. B., Redeker, A. G., and Davis, P., *Amer. J. Med.*, 1958, **25**, 359.
[11] Kiley, J. E., Welch, H. F., Pender, J. C., and Welch, C. S., *Proc. Soc. exp. Biol. (N.Y.)*, 1956, **91**, 489.
[12] —— Pender, J. C., Welch, H. F., and Welch, C. S., *New Engl. J. Med.*, 1958, **259**, 1156.
[13] Schechter, D. C., Nealon, T. F., Jr., and Gibbon, J. H., Jr., *Surgery*, 1958, **44**, 892.
[14] Sherlock, S., *Amer. J. Med.*, 1958, **24**, 805.
[15] Otto, J. J., Pender, J. C., Cleary, J. H., Sensenig, D. M., and Welch, C. S., *Surgery*, 1958, **43**, 301.

potassium, and ammonium in exchange for sodium. Tests on dogs showed that the ammonium levels in the blood fell and the animals suffered no ill effects. Two dogs with acute hepatic ischaemia were treated, with reduction of ammonium and potassium levels and a rise in the sodium level. The apparatus was then used to treat a patient with cervical carcinoma and hepatic metastases who had the clinical features of impending hepatic coma, with deep stupor and "flapping" tremor. The blood ammonium value of 8.22 μg. per ml. was reduced by perfusion to 6.37 μg. per ml. Though the dialysis was considered inadequate, there was complete remission of the patient's symptoms and she became lucid and alert. Heparinization was considered inadvisable for this patient because of the possibility of haemorrhage from the fungating cervical growth, and clotting limited the time during which dialysis could be carried out. This problem of rendering the blood uncoagulable before dialysis is a difficult one in patients with liver disease who already have a bleeding tendency and may be suffering from gastro-intestinal haemorrhage. It is certainly inadvisable to give anticoagulants if bleeding is continuing, but once it has been controlled heparin has been given without ill effects.

These results are clearly only preliminary, but they are important. The cause of hepatic coma is not precisely known. Probably it is the result of a number of noxious stimuli affecting the sensitized brain of the patient with liver disease.[14] Haemodialysis may be effective by removing not only ammonium from the blood but also other, unknown, toxic substances. Dialysis may help to show what those are. The use of an actual donor liver would be more useful than a machine in treating these patients. So far this has been achieved only in the dog. J. J. Otto and his colleagues[15] have successfully perfused an isolated liver with blood having a high content of ammonium from an Eck-fistula dog and shown an 85% extraction rate. The isolated liver was also able to produce bile and to excrete bromsulphthalein from the perfusate. Such a donor organ might remove not only toxic ammonium but also other substances that might be causing the cerebral disturbance.

CANCER OF THE NOSE IN NICKEL WORKERS

The production of nickel by the gaseous carbonyl process began at the Clydach Refinery near Swansea in 1902. The plant was the first of its kind in the world, so that there was no experience to suggest any possible specific occupational hazard except carbon monoxide poisoning. Apart from gassing accidents due to nickel carbonyl gas ($Ni(CO)_4$) there was no general intimation of any adverse effects on the health of workmen arising from the processes until 1932, when J. C. Bridge[1] recorded that during the previous 11 years 10 cases of cancer of the interior of the nose had occurred at this refinery. He commented guardedly that the question of industrial responsibility must remain open, though the very high incidence of cancer in a little-recorded site could not be regarded otherwise than as suggestive. A. J. Amor,[2] at that time the works medical officer, whose name will always be associated with this subject, undertook a complete medical survey of all the workmen, and after a statistical investigation in 1939 Bradford Hill[3] concluded that there was a very heavy excess of deaths from cancer—almost entirely among process workers—at two main anatomical sites, the lung and the nose. Subsequent experience, recently brought up to date in a series of articles by R. Doll,[4] J. Gwynne Morgan,[5] and W. J. Williams,[6] has confirmed the early observations.

Up to December, 1957, 131 cases of cancer of the lung and 61 cases of cancer of the nose had been discovered among workmen employed or previously employed at the plant, which had a works population of about 950 men. As cancer of the lung is quite common in the general population while cancer of the nose is very rare, it has been accepted that the incidence of cancer of the nose is the more reliable index of exposure to a specific carcinogenic agent during the refining of nickel. On the basis of deaths occurring between 1948 and 1956 Doll[4] concluded that the risk of nickel workers in South Wales dying from cancer of the nose and cancer of the lung was significantly increased, particularly so with cancer of the nose.

The first case of cancer of the nose among these workmen occurred in 1923 and of cancer of the lung in 1927. Clinically the cancer begins as nasal inflammation or papillomata or both. The papillomata become malignant and invade nasal sinuses, particularly the ethmoid. Death follows within two years. The cases occurred 6 and 42 years after entry to employment, the peak incidence being in men who had been at this work for 20–25 years. The youngest age at death was 36 years, and the oldest 78 years. While the disease almost exclusively affected process workers, sporadic cases were noted among others.

From the outset of all these investigations urgent action was taken to identify the carcinogenic agent. Suspicion fell mainly on the dusty processes in the

[1] Bridge, J. C., *Annual Report of the Chief Inspector of Factories for the Year 1932*, H.M.S.O., London.
[2] Amor, A. J., *Bericht über den VIII Internationalen Kongress für Unfall medicizin und Berufskrankheiten, Frankfurt A-M., 1938*, vol. 2, p. 941, 1939. Leipzig.
[3] Hill, A. B., quoted by Morgan, J. G., in *Brit. J. industr. Med.*, 1958, **15**, 224.
[4] Doll, R., ibid., 1958, **15**, 217.
[5] Morgan, J. G., ibid., 1958, **15**, 224.
[6] Williams, W. J., ibid., 1958, **15**, 235.
[7] Sunderman, F. W., quoted by Williams, W. J. (loc. cit.).
[8] Hueper, W. C., *Tex. Rep. Biol. Med.*, 1952, **10**, 167.
[9] Løken, A. C., *T. norske Lageforen*, 1950, **70**, 376.

handling of the matte or concentrate of the ore. These processes included calcination, the production of copper sulphate and nickel sulphate, and furnace work. Possible carcinogens were radioactive substances, arsenic, and nickel carbonyl. There is no evidence that the copper-nickel matte is radioactive at any stage of the process. For various reasons, mainly epidemiological, nickel carbonyl is not thought to be the cause of the Clydach cases, though F. W. Sunderman[7] claims to have produced lung cancer in rats by nickel carbonyl inhalation. The problem is further complicated in that deposition of nickel occurs in the lungs, and W. C. Hueper[8] has produced malignant tumours, predominantly sarcomata, at various sites in rats, including the ethmoid, by injections of pure nickel suspended in lanolin. The circumstances of these experiments, however, were very different from those surrounding occupational exposures. A. C. Løken[9] has reported cancer of the lung—but not of the nose—in a Norwegian works where nickel is refined by an electrolytic process in which carbonyl gas is not involved. At the Clydach Refinery before 1921 the sulphuric acid used for extraction of copper sulphate from the matte contained a considerable quantity of arsenic, and indeed Amor[2] had reported cases of arsenical poisoning of a minor degree of severity among the Clydach workmen. Dr. Gwynne Morgan, the present works medical officer, is inclined to regard arsenic as the noxious agent, particularly since new cases of nasal cancer have not been observed among men who began work after 1924, though sporadic fatal cases are still occurring among men engaged between 1902 and 1924. The significance of the year 1924 is that the sulphuric acid used has been practically free of arsenic since that date, and also great improvements in working conditions were then made by ensuring the plants were dust-free. Although some questions still remain unanswered, the alarming occupational hazard to which nickel workers were exposed has been brought under control during the past 35 years, thanks largely to the co-operative efforts of the Mond Nickel Company and H.M. Factory Department.

THE N.H.S. IN 1958

The story of increasing costs in the National Health Service is continued in Part I of the Ministry of Health's report[1] for 1958. The increase—£41m.—was foreshadowed in the estimates and a further rise is expected in 1958–9. The total cost of the N.H.S. in England and Wales for the year ended March 31, 1958, was £626m., and of this £480m., or about three-quarters, was paid by the Exchequer. The balance was met from local rates, Health Service charges, superannuation contributions, transfers from the National Insurance fund, and payments from National Health Service contributions. Under the National Health Service Contributions Act, which came into force in September, 1957, transfers from the National Insurance fund to N.H.S. expenditure ceased and were replaced by separate National Health Service contributions. These were increased in July, 1958, to 2s. 2d. for men, 1s. 8d. for women, and 1s. 2d. for a boy or girl weekly (5½d. of these amounts is paid by an employer), and as a result the cost to the Exchequer of the estimated expenditure of £675m. on the N.H.S. in 1958–9 is expected to fall to 72.4% as against 76.6% in the year under review. In other words, slightly more of the cost will be borne by the direct contributions of people of working age.

Compared with 1957 the cost of the hospital and specialist services went up in 1958 by £23m. to £338.7m. The prices of goods and services purchased increased by about 3½% and wage awards added over £10m. There was, however, greater "productivity," and it is recorded that 3,889,000 courses of in-patient treatment—95,000 more than in 1957—were completed and that 74,000 "day patients" were treated compared with 68,000 in the previous year without any change in the number of staffed beds. Waiting-lists remained about the same at 443,000. Hospital beds were allocated to departments in the following percentages: mental disorder, 44.3; medical, 14.7; surgical, 14.8; chronic sick and geriatric, 12; gynaecology, 2.0; obstetrics, 3.7; general-practitioner units, 2.1; convalescent, 1.6. Private pay beds accounted for about 1.2% of all beds. The average weekly cost of maintaining in-patients with acute disorders in teaching hospitals in London was £33 4s. 2d., and £27 10s. 1d. in the provinces, while the national average for similar cases in non-teaching hospitals was £22 12s. 5d. Tucked away in the report is the news that hospitals in England and Wales purchased 22 million square feet of *x*-ray film in 1958.

The number of general practitioners practising as principals increased from 19,343 in 1957 to 19,599, and 13,253 of them were in partnership, 291 more than previously. The average number of patients per doctor remained about the same at 2,267. Chemists dispensed nearly 4 million fewer prescriptions in 1958, the lowest number since 1949, but their cost, £65,475,490, was over £4½m. more than in 1957 owing to an increase in the average prescription cost of 6½d. to 6s. 5d. The fall in number is attributed to the absence of a serious epidemic during the year and to the continuing effect of the prescription charges introduced in 1956. The increased cost, it is thought, is a consequence of the higher cost of the newer and more expensive drugs supplied. Antibiotics and corticosteroids between them accounted for 34% of the drugs dispensed by chemists for G.P.s.

No striking change in the various fields of the local authority health services is reported. The number of domiciliary confinements (265,215) attended by midwives increased by 9,468 over 1957. In 220,823 of the cases doctors were booked and were present at delivery in 44,964 of them. The proportion of cases in which a

[1] Report of the Ministry of Health for the year ended December 31, 1958. Part I, 1959. H.M.S.O., London. Price 15s. 6d. net.

doctor was booked rose from 81% in 1957 to 83% in 1958. Immunizations of children continued at a steady, if unspectacular, rate. Primary vaccinations against smallpox numbered 421,241, including babies under 1 year of age in numbers equivalent to 44.5% of live births. By the end of the year 46.7% of children under 15 could be regarded as protected against diphtheria, and 470,290 children were immunized against whooping-cough. Forty-one local authorities had included tetanus immunization in their schemes. 1958 was a year of campaigning for poliomyelitis vaccination, and by the end of the year some 6 million children born since 1943 had had two injections of vaccine—60% of those eligible in the age group. Young persons aged between 16 and 25 were slow in coming forward and the response from expectant mothers was also disappointing. The Minister of Health, in his introduction to the report, appeals for the co-operation of the people in benefiting from the health services available to them. "It would be a great gain to the country," he writes, "if, instead of preoccupation with disease and drugs and hospitals, people thought more of preserving good health and acting on the advice available to them on how this may be done."

EPIDEMIOLOGY OF HYPERTENSION AND CORONARY-ARTERY DISEASE

In adult life hypertension and coronary-artery disease share the major responsibility for cardiovascular illness and death, and the World Health Organization's Expert Committee on Cardiovascular Disease and Hypertension has been considering the contribution which epidemiological study can make in this field. A number of important and profitable lines of investigation are apparent. These include studies of the incidence of coronary-artery disease in relation to smoking, physical activity, and diet, but in its first report[1] the committee wisely concerned itself primarily with the task of discovering the true incidence of hypertension and coronary-artery disease in all countries. While there is a firm impression that important differences do exist, the data on which this is based are considered unreliable, since accuracy of death certification varies greatly from country to country, and widely differing nomenclature is used. National vital statistics do not therefore necessarily give the required information, and, while the World Health Organization means to intensify its campaign for improved standards of death certification in conformity with the *International Statistical Classification of Diseases*, the answer to these questions must at present be sought in field studies of populations which can be accurately defined. In order that these may be strictly comparable and the results obtained capable of clear-cut interpretation the committee now presents for consideration and criticism "minimal criteria for diagnosis, definition, and methods of reporting" which it is hoped will be adopted by all engaged in such studies. Little exception in fact can be taken to most of these recommendations, which are clearly the product of much careful thought.

In the epidemiological study of hypertension it is appreciated that only "casual" blood pressure readings can be expected, but the committee thinks these are acceptable provided care is taken to record the "mean" of several readings and to exclude extraneous stimuli as far as possible during the examination. In defining hypertension difficulties are inevitable, but the committee's suggestion that blood pressure below 140/90 mm. Hg is normal and above 160/95 mm. Hg is hypertensive seems reasonable. Some, however, may feel that in a study of hypertension which by definition is diastolic little would be lost, and some embarrassment possibly saved, if for purposes of classification the systolic pressure could be ignored.

The classification of essential hypertension (all known causes having been excluded) as (*a*) uncomplicated, (*b*) complicated, or (*c*) malignant is also commendably simple, but since no mention is made of papilloedema the term "malignant" is here presumed to include all cases of "accelerated" hypertension whether papilloedema is present or not.

For the identification of coronary-artery disease the committee believes that in population studies a clear history either of angina or of myocardial infarction must be obtained and that the term "coronary insufficiency" should be avoided. A history of angina may be recorded as "definite" or "probable," but the varying patterns of symptomatology which may be accepted as justifying this diagnosis are unequivocally defined in the committee's report. The occurrence of sudden unexpected death or of cardiac failure is not regarded as good evidence of coronary-artery disease.

Electrocardiography, if used with suitable precautions and with full knowledge of its limitations, is expected to play an important part in the recognition of coronary-artery disease among large groups of people. The report recommends, however, that electrocardiograms should be interpreted by several observers both before and after access to clinical data. Only recognized changes of actual myocardial infarction (fully defined and classified in the report) should be accepted as evidence of coronary-artery disease. Other commonly found abnormalities such as auricular fibrillation, bundle-branch block, and T-wave changes are less certainly related to coronary-artery disease, and exercise tests, while valuable clinically in suspected cases of angina, are considered impracticable in large-scale studies.

Because of the limitations of the methods which can be used, it is clearly a more formidable task to determine the incidence of coronary-artery disease in a population than of hypertension. As Drs. D. Weitzman and E. B. Smith show in their paper at p. 162 in this issue, symptomless coronary-artery disease is certainly no rarity, and it must be expected that numbers of cases inevitably will escape the net. Nevertheless, provided methods are standardized, the results of epidemiological studies should allow fair comparisons to be made, and it is greatly to be hoped that these worth-while projects will receive the support and co-operation of all countries.

[1] "Hypertension and Coronary Heart Disease: Classification and Criteria for Epidemiological Studies," *Wld Hlth Org. techn. Rep. Ser.*, No. 168, 1959, Geneva.

Drug Treatment of Disease

DRUG TREATMENT OF MALARIA

BY

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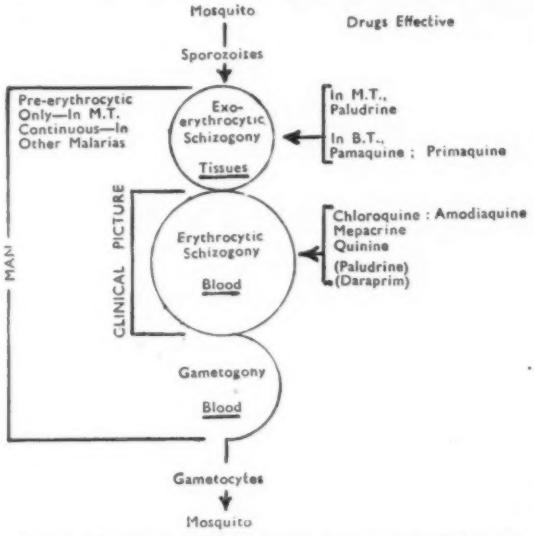
Life Cycle

The diagnosis of malaria rests on the recovery and identification of the parasites. Its treatment is governed by knowledge of the life cycle of the causative parasite. The recognized malaricidal drugs each act at certain points in the cycle of the parasite, not at all points. The diagram below sets out graphically the developmental cycles of the four malaria parasites of man: *Plasmodium falciparum*, causing malignant tertian (M.T.); *P. vivax*, causing benign tertian (B.T.); *P. ovale*, causing ovale tertian; and *P. malariae*, causing quartan (Q.) malaria. M.T. and B.T. are the most prevalent and ubiquitous.



There are two complete cycles and one partial cycle of development of the parasites in man. The first, or tissue phase, occurs in cells of the liver and probably of other organs in all four species during the incubation period of the disease. In B.T., ovale, and quartan malarias this tissue or extra-erythrocytic cycle persists in some form throughout the duration of the infection; it causes the relapses characteristic of these infections, as further infection of the red cells takes place from it. In the case of M.T. malaria alone the tissue phase is pre-erythrocytic only; it vanishes when the red-cell cycle is established; it cannot initiate relapse when the red-cell cycle has been destroyed. The asexual schizogony cycle in the red cells is solely responsible for the clinical manifestations of malaria in man. The gametogony cycle, arising from this blood cycle, ends with the formation of the pre-sexual gametocytes, which circulate in the blood merely to infect mosquitoes; they cause no inconvenience to their host.

Treatment of Clinical Attack

The arrest of acute uncomplicated malarial fever is readily achieved by the oral administration of one of the following drugs, which are listed in order of preference, with their dosage.

Chloroquine and Amodiaquine.—These are 4-aminoquinolines; the former is the more generally used. Chloroquine is sold in tablets of the diphosphate (250 mg. containing 150 mg. base), or sulphate (204 mg. containing 150 mg. base). An initial loading dose of 600 mg. base is followed after six hours by 300 mg. base, and thereafter by 300 mg. base on each of another two days.

Amodiaquine ("camoquin") is put up in tablets of the dihydrochloride dihydrate salt, each containing 200 mg. of the base. The loading dose is 600 mg. base; then 400 mg. base is given daily for two days.

Both drugs are absorbed rapidly, localized and slowly metabolized in the tissues, and excreted slowly. The toxicity of either in these doses is negligible and there are no contraindications to their use.

Mepacrine is an amino-acridine sold in tablets of the dihydrochloride dihydrate (100 mg. containing 78.5 mg. base). The dosage is 2 tablets (200 mg. salt) 4 or 5 times on the first day, followed by 1 tablet (100 mg. salt) thrice daily for another six days.

Mepacrine stains the skin yellow; it may cause colic and diarrhoea, nausea, and vomiting in those not habituated to it. In some cases mental changes, even maniacal, may attend its use. It is falling into disfavour for these reasons, and also because it increases the toxicity of the 8-aminoquinolines (see below) when given in association with them.

Quinine is sold as tablets of the sulphate, hydrochloride, bisulphate, or dihydrochloride. The first of these salts is virtually insoluble, the last very soluble. Absorption is rapid, so loading is not necessary. The dose is 10 gr. (650 mg.) of the sulphate, or other salt, thrice daily for five to seven days.

Quinine is bitter; it causes giddiness, tinnitus, and deafness in those not habituated to it. Graver symptoms may follow gross overdosage. Prescribing of it has fallen off owing to the introduction of the synthetic antimalarials, and to an exaggerated fear of its precipitating blackwater fever in cases of M.T. malaria. It is a safe and efficient drug for the control of fever due to any malaria parasite, provided that the patient has not previously been taking the drug irregularly.

In addition to these *proguanil* ("paludrine"), which is a biguanide, can be used as the monohydrochloride in tablets each containing 100 mg. (87 mg. base). Its action on the erythrocytic cycle is slow, as is the clinical response. It therefore is not satisfactory for clinical cure, but is reserved for prophylaxis, for which purpose it is excellent. Proguanil is devoid of toxicity in any advocated dosage. *Pyrimethamine* ("daraprim") resembles proguanil in most respects therapeutically. Inadequate dosage with either of these drugs results in a strain of parasites resistant to both of them.

Eradication of the Infection

In M.T. malaria thorough treatment of the acute attack, as already indicated, leads to destruction of the erythrocytic forms of the parasite and so eradication of

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the infection. In the other types of malaria the continuing exo-erythrocytic cycle must be destroyed, as the drugs which control the clinical attack do not affect this cycle. The drugs which destroy the exo-erythrocytic cycle are given orally either concurrently with, or immediately after, treatment of the clinical attack. They are the following 8-amino-quinolines:

Pamaquine.—This is sold in tablets of the monohydrochloride (9 mg. containing 8 mg. base), or dihydrochloride (10 mg. containing 8 mg. base), or naphthoate (18 mg. containing 8 mg. base). The dosage is 8 to 10 mg. of the base thrice daily for ten days.

Primaquine.—One tablet of the diphosphate (13.5 mg. salt containing 7.5 mg. base) is given twice daily for ten days.

These two compounds may cause severe side-effects in the form of nausea, abdominal cramps, methaemoglobinaemia, cyanosis, and the passage of dark urine. Neither should be given in association with mepacrine, as this drug aggravates their toxicity. Patients taking them are best in hospital.

Treatment of Grave or Complicated Attack

M.T. malaria is so called because it may rapidly fulminate and give rise to grave complications commonly due to obstruction of small vessels, particularly in the brain, by parasitized red cells. In such cases speed and certainty in the control of the infection are imperative if life is to be saved. The advocated methods of oral treatment are entirely satisfactory if the patient is conscious and he can swallow and absorb the drugs. Often in pernicious malaria he is vomiting; he may be mentally deranged or comatose. Parenteral treatment is then necessary. The drugs used under such conditions in order of choice are:

Quinine Dihydrochloride.—7.5–10 gr. (500–650 mg.) of this freely soluble salt is given intravenously slowly (over 10–15 minutes), preferably well diluted in normal or glucose saline, and an intravenous saline drip is set up. It may be necessary to repeat the dose in the same manner after eight hours, and again after another eight hours, but this is rarely necessary. Oral treatment should replace the parenteral treatment at the earliest opportunity. After giving the initial intravenous quinine, treatment with chloroquine by mouth may be substituted. Quinine injected intramuscularly is prone to cause local necrosis.

Chloroquine Diphosphate.—200–400 mg. of the base is given intravenously in 500 ml. of normal or glucose saline over a period of one hour; another 200 mg. base is given after eight hours if occasion demands. Alternatively, 200–300 mg. base is given intramuscularly, and repeated after a similar interval if necessary. Intramuscular injection of chloroquine is quite effective and may be thought preferable to intravenous administration.

Mepacrine Dimethanesulphonate.—120 mg. in an ampoule is equivalent to 100 mg. of the dihydrochloride dihydrate. In default of one of the preceding two drugs, 200 to 300 mg. of this soluble salt may be given intramuscularly (not intravenously), and repeated at eight-hourly intervals if imperative. Mepacrine intramuscularly can give rise to considerable abscess formation, and it is better avoided in favour of quinine or chloroquine injections.

Semi-immune Persons

The indigenous inhabitants of countries where malaria is endemic, who have survived long-continued and repeated infection with the local strains of parasites, become tolerant of their infections and do not suffer the severe clinical manifestations to which new entrants are subject. When their infections do trouble them, one or two doses of any of the drugs effective against the erythrocytic infection will relieve them. Sterilization of their infections may be undesirable, because it results in a loss of their tolerance.

Prophylaxis and Suppression

Residents of non-malarious countries travelling to malaria-endemic areas should practise drug prophylaxis. There is no causal prophylactic which destroys the infective sporozoites injected by the mosquito. Proguanil and pyrimethamine, if taken regularly, will destroy the ensuing tissue or pre-erythrocytic stage of M.T. malaria, and so will sterilize this infection before it becomes erythrocytic. Neither they nor the other drugs available will do this in the case of B.T. and the other malarias. Any of the drugs acting on the erythrocytic cycle if taken consistently will prevent its development, or keep it at so low a level that it fails to cause clinical manifestations. This is therefore only suppression, or clinical prophylaxis. Proguanil and pyrimethamine are valuable for this purpose, especially in view of their specific effect on the very early M.T. infection. The drug selected must be taken with unfailing regularity. Those recommended and their doses are as follows:

Proguanil.—100 mg. daily, starting a week before arrival and continuing until 30 days after leaving. An allied preparation—lapudrine—has just been put on the market. It is said to be more persistent, so once-weekly dosage with this preparation is adequate. Alternatively, *pyrimethamine* may be given, 25 mg. once weekly. Strains of parasites can develop resistance to proguanil and pyrimethamine. Though rare and local, where such strains exist these drugs obviously should not be relied on.

Chloroquine.—300 mg. (base) once weekly, or *amodiaquine*, 400 mg. (base) once weekly.

Mepacrine.—100 mg. daily. Its yellow-staining tendency militates against its use.

Quinine should *not* be used as a chemoprophylactic if the other drugs are available; if they are not, the dose of quinine is 5–10 gr. (320–650 mg.) daily. Quinine is not an efficient chemoprophylactic or suppressive; where M.T. malaria is endemic, its use for this reason is associated with an increased incidence of blackwater fever.

Dosage Scales

The doses given for treatment are appropriate to normal adults weighing 9 to 12 stones (57–76 kg.). They can be adjusted by the usual age scales for children, with an increase on the generous side. The prophylactic, or suppressive, dosage for children can safely and with advantage be given at a higher level than the age scales would indicate. For heavy adults the therapeutic dosage should be rather higher and the prophylactic dosage should be double for those over 14 stones (88 kg.), as it can also be for normal persons subject to unusually heavy exposure to infection.

GENERAL MEDICAL ASPECTS OF CONFUSIONAL STATES IN ELDERLY PEOPLE*

BY

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Mental confusion has been defined as "a condition in which those notions persons ordinarily have of their relations with time and space and of their own personalities become less clear, perhaps to such a degree that the patients, though conscious, no longer recognize their surroundings or realize their own identity. Associated with this inhibition of the action of high psychic centres there may be a removal of restraint upon lower and more automatic ones, so that agitation, excitement, and hallucinations take the place of orderly conduct, equable affective tone, and true perceptions" (Macnamara, 1933). Implicit in this, and in any acceptable definition of mental confusion, are tenuity of contact with reality, and clouding of the patient's awareness of his own personal identity and of himself in relation to his environment.

A Misuse of Words

Mental confusion is to be clearly distinguished from dementia, and to equate the two is at best a misuse of words and their meaning. The fact that dementia and mental confusion may be seen together in the same person is fortuitous, not obligatory; a demented patient is not necessarily confused, nor is a confused individual by any means necessarily demented. It is most unfortunate that the two terms are so often used synonymously; and this is particularly so in dealing with old people. For dementia, and especially when qualified by the adjective "senile," carries a connotation of hopeless and irreversible mental dissolution, of itself unjustified, but to be condemned in the strongest possible terms when extended to include confusional states, whether qualified as "senile" or not. This inexcusable practice is due not only to woolly definitions but also, and more importantly, because of ignorance concerning the mental changes normally to be expected in old age and inseparable from the process of normal senescence.

Senile Dementia

With advancing years everyone undergoes a mental as well as a physical decrescence, and in old age people are less than they were in almost all respects—in range of interests, memory, intellect, emotional control, etc. In that they are old people, and have suffered a "deterioration in total personality and mentality," they may, by strict definition, be diagnosed "senile dementia." But to diagnose the majority of elderly people as dements on this score is nonsense and humiliating, misleading, and hurtful. Psychiatrists have long recognized that in practice no sharp line can be drawn between senile dementia on the one hand and the normal mentality in old age on the other: the one merges imperceptibly with the other, and the diagnosis is made on social rather than on psychological grounds. Broadly, if the aged individual adequately fits into his customary surroundings he is usually, and rightly, considered to be "normal."

It is a well-recognized fact, however (which should not prejudice the foregoing), that many old people who are quite acceptable, and accepted, in their accustomed surroundings can nevertheless be shown to have a considerable degree of dementia. The elderly lady of good social and financial standing who is forgetful of names and unaware possibly even of the time of day is known to us all. By deeply ingrained habit and training she produces the appropriate phrase or action automatically, and maintains herself quite adequately in her environment provided that no unusual or excessive demands are made upon her. Ordinarily, medical advice is not sought for such people because they present no problem (unless an accident such as a fire caused by forgetfulness or a petty misdemeanour of similar cause puts them "beyond the pale"). Such persons are commonly to be found in all strata of society and throughout the whole community, living at home and accepted without question by their families and friends. But, seen for the first time by someone who is not accustomed to their foibles and peculiarities, they could well be labelled "senile dements." If by this diagnosis it is implied that they should properly be housed in an asylum, nothing could be further from the truth, for such persons can continue indefinitely, harmoniously and appropriately, within their own accustomed environment.

Mental Confusion: A Different Picture

But how different is the picture in mental confusion; for now the whole equilibrium is shattered. A behavioural disorder, such as restlessness, nocturnal wandering, and incontinence of urine or of faeces, destroys the environmental balance (much more certainly than hallucinations and delusions), and medical attention is urgently sought. But what is diagnosed is "senile dementia"—in this context an irrelevant and valueless description applicable to almost any old person, entailing the sinister implication of a hopeless and irreversible mental disease for which immediate (and permanent) admission to a mental hospital is requested and expected. The root cause of the crisis is not adequately sought, for the meretricious diagnosis will solve the immediate problem. It is not sufficiently appreciated that the confusional state is probably quite transitory, and that, if its precipitating cause is found and can be remedied (or when it has spontaneously ceased to be effective), the patient will probably revert, quite rapidly or within a reasonably short time, to her former state, in which, let it be remembered, "demented" though she may have been, she was living at home, or elsewhere, in reasonable harmony and equilibrium with her customary surroundings.

These pathetic cases are very common and justify three injunctions: first, to study the natural history of mental ageing; second, to appreciate that confusional states in elderly people are potentially reversible and usually of good prognosis; and, third, to act accordingly until time proves us wrong.

I have laboured this point because I believe it to be the fundamental reason for the otherwise inexplicable attitude of so many competent and well-intentioned

*Read to the Sections of Geriatrics and Psychiatry at the Annual Meeting of the British Medical Association, Birmingham, 1958.

physicians and surgeons to many elderly patients. For, granted the belief that a case is hopeless, a shrug of the shoulders and a prescription for hypnotics become less incomprehensible; "the old dog has had his day," and the problem resolves itself into how best to dispose of the mental corpse.

I would strongly urge that no elderly patient should be admitted to a mental hospital as a case of "senile confusion" or "senile dementia" without prior investigation by an interested physician in a general hospital or in the acute wards of a geriatric unit fully equipped to deal with such problems. I do not deny—indeed, the contrary is the case—that the mental hospital should play an important part in the short- and long-term management of psychiatrically disordered old people; but it is my firm belief, based on a knowledge of not a few of them, that most mental hospitals in this country to-day are burdened with large numbers of old people who—whatever the original reason for their admission—should properly not be there at all. Elderly patients should occupy mental hospital beds only when they are likely to respond to specialized psychiatric treatment, or when severe and persistent behaviour disorder makes mental hospital nursing and management imperative. This is not an unattainable ideal but quite a practicable objective, as experience in Oxford has demonstrated (Cosin *et al.*, 1957).

The magnitude of the problem of confusional states in elderly people is shown by the fact that no less than 80% (4,000) of the 5,000 patients aged 65 or more who were admitted in the past eight years to the Oxford Geriatric Unit were mentally confused, whatever their salient diagnosis or other clinical condition. (It should be noted that the acute Geriatric Unit at Cowley Road Hospital in Oxford is a general medical establishment for the diagnosis, treatment, and subsequent disposal of elderly patients: admissions are largely unselected except on the grounds of age, and over 85% come direct from home. It is not a psychiatric institution as such; and there is no reason to suppose that the very high incidence recorded here of mental confusion in general illness in old age is in any way peculiar to Oxford.)

A Common Complication of Disease

Mental confusion is so commonly seen as a complication of so many and such a wide variety of diseases in elderly patients as to be regarded in practice as virtually a "normal" accompaniment of any illness in old age, whether psychiatric or somatic and however remote from the brain the primary disturbance may be.

It follows that "senile confusion" must be regarded, not as a diagnosis (a disease *sui generis*) but only (like cough or abdominal pain) as a symptom, which demands elucidation before a diagnosis can properly be made.

It is pertinent to inquire why mental confusion is so often a concomitant of disease in old people, and why, although not rare at any time of life, it is so very much more common in old age.

The following are some of the reasons:

1. The human brain is extremely vulnerable to anoxia (Courville, 1939; Hoff *et al.*, 1945; Corday *et al.*, 1953) because cerebral metabolism is completely dependent for its energy reactions on the aerobic combustion of glucose (Himwich, 1951). It is probably more sensitive to oxygen deprivation than is any other organ or tissue in the body (with the possible exception of the liver), and so is the first to be affected—and subsequently the most severely—by hypoxia, however incurred.

2. The supply of oxygen to the brain is dependent upon the state of the heart, the lungs, the blood, and the blood vessels; the composition of the respiratory gases; and the integrity of such homoeostatic mechanisms as the sino-aortic and spinal baroceptor reflexes (Heymans, 1950; Heymans and Delaunois, 1951; Heymans and Heuvel-Heymans, 1951).

3. Disordered cerebral function is probably more readily apparent, either subjectively or objectively, than a similar degree of functional impairment in any other organ in the body.

4. Although opinions differ about the true relationship between mind and brain, and although many psychopathological states occur in the absence of structural cerebral abnormality, few would maintain that derangements of cerebral cellular metabolism, entailing as they do disturbance of function of the cells of the brain, will not also adversely influence the functions of the mind.

Cerebral cellular metabolism, as well as being wholly reliant upon oxygen and glucose for its energy reactions, is also dependent upon a supply correct in amount and proportion of electrolytes, including sodium, potassium, calcium, hydrogen, and phosphorus, and of substances including water, amino-acids, fats, glucose, enzymes and co-enzymes, and vitamins: all these in turn are dependent upon the state of the liver and of the kidneys, the endocrine glands, the intestines, and the amount and composition of the diet (Danowski and Elkinton, 1951; Holley and Carlson, 1955; Bedford, 1957a).

Thus each and every one of the organs and systems of the body is directly concerned in cerebral cellular metabolism, and a disturbance of function of any may lead to adverse cerebral and mental effects.

Factors Explaining Mental Confusion in the Elderly

The foregoing considerations apply to young and old alike and go some way to explain why mental confusion may be a complication of disease at any time of life. Some additional factors which explain its excessive frequency in the elderly are the following (they are some of the many direct consequences of senescence):

1. The cerebral circulation tends to become impaired in old age, and the brain is therefore more vulnerable in the elderly to the effects of anoxia (Himwich, 1951) and of disease in other systems (Bedford, 1956a, 1956b, 1957b).

2. In old age, derangement of function of all organs occurs more readily because their "reserve" is lowered as a result of tissue and cellular ageing effects and of the damage done by previous disease.

3. With advancing years, episodes of illness, especially infections of the respiratory and urinary tracts, tend to occur with increasing frequency, each episode carrying the hazard of cerebral metabolic or structural disturbance and mental confusion.

It is therefore not surprising that the brain in old age is a sensitive "indicator" of disordered function anywhere in the body, and that mental confusional states are so commonly seen in geriatric practice. These reasons also explain why mental confusion is a non-specific symptom in the sense that the same picture may be produced by widely different aetiological factors: thus it has been impossible to relate any particular

pattern of mental confusion to its organic cause; for infections, heart failure, uraemia, etc., may produce precisely similar mental reactions.

In discussing the somatic—that is, physical or structural—aspects of mental confusion, the importance of the adverse psychological effects of ageing in the aetiology of mental confusional states must not be minimized. Failing vision and defective hearing, tinnitus and giddiness, limitation of physical activity, the death of relatives and friends, increasing loneliness and diminished contact with society—all these conduce to a highly precarious mental state hovering on the brink of confusion. The extreme vulnerability of a mind in this state to further insult—both psychic and somatic alike—cannot be overemphasized.

Diagnostic Approach

The diagnostic approach to confusional states in elderly people should be governed entirely by the principle that "senile confusion" means no more than that "this old person is ill." It implies that a worthwhile history is unlikely to be forthcoming and that he or she may present some difficulties in management for a while—but no more than that. The fact that a great many well-adjusted elderly people show some degree of mental impairment should be kept constantly in mind lest the automatic label of "senile dementia" be allowed unduly to influence the issue.

Diagnosis, then, embraces virtually the whole of medicine—general and psychological, and including surgery and gynaecology—and demands the exercise of no more peculiarly specialized skills than does paediatrics (of the same order and for very similar reasons). Precisely the same rules apply, but it will perhaps bear repetition that in elderly patients multiple diagnoses are the rule rather than the exception and that evidence of disease in one system by no means precludes the fact that another is at fault. A taxonomical guide to the diagnosis of confusion in elderly people has been given elsewhere (Bedford, 1954).

Management and Prognosis

In every phase of management it is important to bear in mind that confusional states (as distinct from dementia) in the elderly are potentially reversible once the cause, or causes, has been remedied or has otherwise ceased to be effective. This is shown by the fact that in my series of cases the mental confusion lasted for less than one month in all but 18%, and for more than six months in less than 6%.

The prognosis of confusional states in the elderly with regard to life is essentially that of its cause; and as regards mental recovery is not (perhaps surprisingly) materially affected by the degree of pre-existing mental impairment except in extreme cases. The high mortality rate in my confused patients (33% of them dying within a month after the date of their admission to hospital) is no different from that of the patients who were not confused, and simply reflects the gravity of severe illness in general in old age (Bedford and Caird, 1956); (many cases were admitted in a terminal condition).

In the large majority of cases the confusional state was transient, and the patient recovered within a week or two (and in a few cases immediately) once the cause had subsided. Recovery, however, was sometimes considerably delayed, and on occasion persistent or incomplete (as is seen in cases of head injury). This is not surprising when one reflects how much is entailed in an elderly patient's rehabilitation after a period of confusion in hospital. For rehabilitation involves a great deal of readjustment. New things, new faces, and new surroundings are seen and must be recognized, memorized, and assessed. Old and once familiar objects must be given their former perspective. Bodily weakness must be overcome and the ability to walk again may demand a long and arduous programme of physical retraining. These adjustments—rapid and automatic in young people—have often to be regained slowly, painfully, and step by step in old age. For old people have everything against them; their ability to learn is slow, while structural cerebral vascular change militates against the ready impress of new engrammata implicit in learning (Welford, 1950; Himwich, 1951; Bedford, 1954). Physical frailty is a further handicap; and it is small wonder, therefore, that recovery after confusional states in the elderly may be slow and sometimes incomplete. On the contrary, it is rather surprising that recovery ever does take place—let alone so frequently, so rapidly, or so completely.

These fortunate outcomes, however, are only rarely spontaneous: they demand the application of the utmost vigilance and energetic treatment during every phase of the care and management of a mentally confused old person. The attitude of all concerned must be one of enthusiasm and cautious optimism: there is no justification for diagnostic or therapeutic nihilism. Any opinion implying that a patient is "too old for . . ." whatever would otherwise be indicated—either diagnostic or therapeutic—must be neither offered nor accepted without very close critical analysis. For what purports to be a reasoned and knowledgeable opinion is all too often in fact just an *ex cathedra* affirmation of an intuitive belief, emotionally charged, ill-informed, and often mistaken. Such misconceptions, however well intentioned, are no longer admissible in the light of the great improvements attainable to-day in the prognosis of diseases in old age.

Summary and Conclusions

"Dementia" and "mental confusion" are entirely distinct clinical entities. Serious errors in dealing with old people arise by confusing these terms, and from insufficient knowledge of the "natural history" of normal senescence.

Mental confusion is an extremely common complication of any disease in old people. This is because the many adverse consequences of old age itself—structural, functional, psychological, and environmental—enhance the extreme vulnerability of the brain at any age to hypoxia, biochemical derangements, and the effects of disordered function in other systems.

"Senile confusion" is not a diagnosis but only a symptom of almost any disease within the whole field of medicine.

The prognosis in senile confusional states is that of its cause as regards life; and as regards mental recovery very hopeful except in extremely demented cases.

(Continued at foot of next page)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Badional Gel (Farbenfabriken Bayer (F.B.A. Pharmaceuticals)).—This contains 10% *p*-aminobenzene sulphonylthiourea—that is, an equimolecular compound of sulphanilamide and thiourea. It is in a neutral gel, and is intended for application to infected wounds and burns and to areas of skin attacked by various kinds of bacterial infection. The film spread over the affected area dries and takes the place of a dressing as well as exerting an antibacterial action.

Urea has some antiseptic action, and has been used in the past for the local treatment of sepsis. Later there was a vogue for using mixtures of urea and sulphonamides in a similar way, and this preparation is a variant of that method, the two elements being combined in a single chemical compound. Advantages which have been claimed for it are greater activity against streptococci and staphylococci than that of sulphonamides alone, activity in the presence of sulphonamide inhibitors, and bactericidal as distinct from bacteriostatic action. On the other hand it is less active than some sulphonamides against Gram-negative organisms, and, like them, affected by the density of the bacterial population.

There is not yet enough published evidence to assess the therapeutic qualities of this preparation in relation to those of many others, including preparations of antibiotics.

N.H.S. basic price.—20-g. tube, 3s. 6d.

(*Continued from previous page*)

The management of confusional states in elderly people calls for the closest collaboration between general hospital, mental institution, and geriatric unit, each playing its respective part; and demands that nothing of possible benefit, having regard to all the advances made in medicine in recent years, be denied to the old on the grounds of their age alone.

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Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Tobacco Amblyopia

SIR,—We would like to make some corrections and additions to your annotation on tobacco amblyopia (*Journal*, June 20, p. 1582). Your statement that "there is no record, however, of cigarette smoking causing the disease" is certainly not true. Traquair[1] reported that this condition may, on rare occasions, occur in heavy cigarette smokers, and Schepens[2] found during the second world war that undernourished Belgians quite commonly developed severe tobacco amblyopia even if they smoked fewer than 25 cigarettes a day. You further state that "in rare cases amblyopia may occur from ingestion of alcoholic drinks in large quantities but without the smoking of pipe tobacco." In support of this view you quote only the case presented by Quatermass,[3] but you failed to indicate that this particular patient smoked ten cigarettes a day. We have also seen two cases of tobacco amblyopia in cigarette smokers: both patients were female and used to heavy drinking. We therefore consider that your annotation would have been more accurate if it had stated that tobacco amblyopia is rare in cigarette smokers but when it does occur some additional factor such as malnutrition or excessive consumption of alcohol is usually present.

The results of our study of 14 male patients with tobacco amblyopia seen at the Bristol Eye Hospital clearly showed that an essential feature was a low vitamin B_{12} concentration in the serum.[4] Other clinical manifestations of vitamin B_{12} deficiency may be absent because, in pipe smokers and heavy cigarette smokers, the amblyopia may precede the onset of anaemia, glossitis, neurological involvement, or megaloblastic bone marrow by months or even years. We also presented evidence that tobacco amblyopia and the retrobulbar neuritis of Addisonian pernicious anaemia may be one and the same condition. In persons with even mild vitamin B_{12} deficiency, as may occur in the "pre-pernicious anaemia" state, malabsorption syndromes, or in "vegans" with a dietary deficiency of vitamin B_{12}, the retina or the optic nerve is unduly sensitive to tobacco.

Finally, you write that "the main treatment is complete withdrawal of tobacco" and "the administration of vitamin-B complex may be of value in speeding recovery." In our clinical trial the effect of parenteral vitamin B_{12} (cyanocobalamin) in improving visual acuity and completely reversing the changes in the visual field was most encouraging, even if the use of tobacco was continued.—We are, etc.,

Institute of Ophthalmology, London. J. M. HEATON.
Torbay Hospital, Torquay. A. J. A. MCCORMICK.
St. Margaret's Hospital, Swindon. A. G. FREEMAN.

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Burn from Electric Blanket

SIR,—A recent case illustrates an unusual type of burn due to an electric blanket. The patient, a known diabetic, had an attack of hypoglycaemic coma at home while lying on an electric blanket. When he recovered consciousness his left thigh had been burned, and this proved to be full thickness over an area of 8 × 7 in. After the accident the blanket had a small area of charring of the outer sheet cover and a larger char over one of the heating wires in the element enclosure. The patient's pyjama trouser was only slightly damaged. This was probably due to his having been perspiring profusely, so that both pyjamas and blanket were soaked with sweat.

Electrical examination of the blanket showed that with the switch in the low position, as it was at the time of the accident, the wiring was still intact and gave a resistance of 1,400 ohms. This corresponds to a consumption of about 40 watts at 240 volts, which only produces a just perceptible warmth over the whole blanket, clearly insufficient to cause cutaneous burning. However, moistening of the charred area with a little distilled water caused the resistance to fall within a few minutes to about 600 ohms. The extra 60 watts was clearly being dissipated in the soaked area, which rapidly became warmer. A similar experiment repeated over a remote area of the blanket with distilled water failed to cause any reduction of resistance, whereas soaking of another similar area with normal saline caused a reduction of resistance like that found at the site of the char. (Areas were chosen for test such that two adjacent wires with a high voltage difference were soaked at the same time, as had happened at the site of the burn.)

It thus appears highly probable that the blanket, either on this or on previous occasions, had become locally soaked with an electrolyte solution, such as sweat, and that this reduced the insulation between heating wires carrying a high voltage difference, producing a local area of heating sufficient to cause burns. The fact that this could be reproduced by subsequent soaking with distilled water indicates that the fabric was impregnated with electrolyte. The experiments on areas previously not apparently exposed to soaking confirm that this mechanism is feasible.

The blanket in question, though apparently not conforming to British Standard B.S. 2612, "Electrically Heated Blanket for Domestic Use," was of a usual design, and an accident such as this could occur with other patterns examined if soaking with electrolyte was sufficiently prolonged. It is therefore unwise to use blankets in circumstances where they may be exposed to profuse sweating or incontinence, particularly when attacks of unconsciousness are possible. B.S. 2612 requires that warnings to this effect be given in operating instructions. A further desirable safety feature would appear to be a change in layout of the wiring whereby heating elements with a high potential difference do not run adjacent. This should lessen the risk of local overheating resulting from reduced insulation.—We are, etc.,

J. P. BULL.
J. S. CASON.

Medical Research Council Burns Research Unit,
Birmingham Accident Hospital.

PAM

SIR,—In the letter by Dr. E. F. Edson on the treatment of organophosphorus poisoning (*Journal*, June 6, p. 1476), pyridine-2-aldoxime methiodide is being referred to as PAM. Your attention is drawn to the fact that PAM has, for ten to eleven years, been the generally accepted abbreviation for procaine penicillin in oil with aluminium monostearate. This is borne out by the extensive literature published on the subject.

Our attention has been drawn to the confusion which may arise from the same abbreviation being now applied to another drug, and in order to be helpful in this question it is suggested that in the future the penicillin preparation be referred to as "penicillin PAM." You may wish to point this out to your readers.—I am, etc.,

Geneva. T. GUTHE,
Chief Medical Officer,
Venereal Disease and Treponematoses
Division of Communicable Diseases,
World Health Organization.

SIR,—In a letter on the treatment of organophosphorus poisoning (*Journal*, June 6, p. 1476) the value of pyridine-2-aldoxime methiodide (PAM) is discussed. In this country, India, PAM is always taken to indicate penicillin aluminium monostearate.

It seems to me exceedingly dangerous to have two entirely dissimilar preparations being described by identical abbreviations. I do not know whether penicillin aluminium monostearate is now being at all widely used at home, but if it is could the manufacturers be asked not to use these abbreviations in their descriptions of either preparation?—I am, etc.,

Ramnad, S. India. M. G. JONES.

Survival After Cardiac Arrest

SIR,—I was interested to read the case report of survival following cardiac arrest, by Dr. C. A. B. Clemetson (*Journal*, July 4, p. 14), and the comment that cardiac massage should be attempted outside an operating theatre. A more useful observation might have been the danger of chloroform anaesthesia.

When I was an obstetric house-surgeon we had a similar case following chloroform, administered on the district. Pulsation was fortunately restored by intracardiac adrenaline without opening the chest. Since this incident chloroform has not been part of the Bradford flying-squad equipment; open ether is used very successfully.—I am, etc.,

Bradford, Yorks. K. W. SWEETING.

SIR,—I was most interested to read the article entitled "Survival after Cardiac Arrest," by Dr. C. A. B. Clemetson (*Journal*, July 4, p. 14). It was truly formidable, and I applaud the efforts of all concerned. Though it is easy to be wise after the event, I was always taught never to give chloroform to a nervous or excitable patient, as rapid collapse and death can occur through cardiac inhibition.—I am, etc.,

South Shields. F. H. ROBSON.

SIR,—The interest in Dr. C. A. B. Clemetson's report (*Journal*, July 4, p. 14) is in the survival of this patient after 8 minutes of gross hypoxia, due surely not to lack of equipment but the failure to apply first aid. Can artificial respiration really only be performed with oxygen and an endotracheal tube? Surely this crisis called for mouth-to-mouth respiration.

I have recently had a similar experience using chloroform on an obstetric patient in a small hospital in India where no oxygen or tube was available. Cardiac arrest occurred during induction. But during the brief interval in which the surgeon was preparing to open the chest the patient was inflated with air, using

a simple mask and bellows. Fortunately the heart restarted, but had cardiac massage been needed at least it would have achieved its purpose of moving oxygenated blood to the vital organs.—I am, etc.,

London, W.1. R. HUTCHINSON.

Qualification in Medicine

SIR,—Having qualified 12 years ago on the rather despised but sensible and down-to-earth Conjoint Board examination, I have recently had occasion to take the London M.B., and I feel that a few observations would be pertinent.

In the M.B. I was asked nothing whatever—either directly or indirectly—at any stage of the examination on such vitally important subjects as the following: antenatal care, management of infants, diet, the exanthemata, ear, nose, and throat disease, eyes, hypertension, diabetes, cardiac ischaemia, peptic ulcer, skin diseases, common nervous ailments, minor orthopaedics, or minor injuries and burns. Instead, the written papers contained questions on malignant tumours of bone, actinomycosis (!), descent of the testicle, meconium ileus, biochemistry of pyloric stenosis, ascites, purpura, the reticulo-endothelial system, and even the design of a therapeutics trial.

The orals were conducted with great courtesy by the examiners, who, however, appeared slightly bored and fatigued by the whole farcical procedure—there were six written papers and nine orals and clinicals for each candidate. The obstetrics viva was almost exclusively on antique instruments "out of the museum," that on pathology almost entirely on tetanus and its prophylaxis, and the medicine viva opened, and remained for the most part, on hookworm in immigrant Jamaicans. This sort of thing might be excusable if the examiners meant to fail a candidate or to give a distinction out of hand, but since they did neither I presume this is the normal methods they use.

If so much stress is to be laid on the examination system in this country, and if a candidate's whole future is to be judged thereby, it is clear that a radical revision of the whole silly process is long overdue. Study might begin with American methods, where the idea would appear to be to encourage candidates with either real or potential ability—not to wreck their nerves. Let the qualifying diploma be "M.D.," whatever the examining body, and let State certificates be available to any candidate who cares to work up a specialty further by postgraduate study, reserving the Royal College higher diplomas for the exceptionally able and experienced. The award of a university M.D. on qualification might do much to give badly needed respect to doctors who appear to have lost it since the war.—I am, etc.,

Welwyn Garden City, Herts. G. O. MORSE.

Vulval Varicosities in Pregnancy

SIR,—As I was the first to start the elastic pants discussion in my letter in the *Journal* of May 2 (p. 1185), may I answer Dr. Beatrice Turner's criticism (*Journal*, June 20, p. 1591)?

My patients tell me that the elastic pants can be washed and even boiled without harm. The manufacturers' "blurb" insists on frequent washing to preserve elasticity. After all, only the gusset need be washed every day, or a folded piece of gauze discarded as often as need be.

I have not encountered any case of pruritus due to the pants, even during a hot summer in obese patients. The overall elasticity of the pants allows them to adjust themselves to the gradually changing contours of the patient up to term. The discomfort of a sanitary towel is well known, and during the last three or four months of pregnancy must be unbearable.—I am, etc.,

Bexleyheath, Kent. A. KOBY.

Water Intoxication

SIR,—A case of this kind will be of general interest owing to its rarity, even in mental hospital practice, where the present observations were made.

Two female psychopaths, aged 32 and 47, and nursed in a closed ward, became aware of a newspaper article in which cases of water addiction were mentioned. They gathered from this that it might be possible to get drunk on water, and promptly proceeded to satisfy their longing for alcoholic oblivion by these inexpensive means. The younger of the two women gave up after 16 glasses of water, having developed a headache. The older one persevered in spite of the vomiting which developed in time. The exact amount of water taken by this patient can unfortunately not be ascertained, as she claims to have no recollection after the tenth glass. It is, however, known that she was aiming at 30 pints (17 litres).

At 6.30 p.m. on Saturday she was reported to have had an epileptic convulsion. Following this she was found to be in a confusional state. She failed to respond to address, misinterpreted touch stimuli, and went through the motions of writing without pen or paper as if composing a letter. There were no other neurological abnormalities then. A further convulsion, as well as vomiting, occurred at 11 p.m., following which she became comatose, with extensor plantar responses and failure to respond to any stimuli at all. There was danger of aspiration of vomitus, and in order to control the convulsions she was given 5 ml. of paraldehyde intramuscularly as well as 1 ml. of mersalyl to promote diuresis.

She was incontinent of copious amounts of urine during the night, and by Sunday morning the level of consciousness, although higher, was still impaired to the extent of uncooperative mutism. She was, however, able to stand on her feet. The pupils responded to light and the plantar responses were flexor. At 6 p.m. she was able to speak, although her speech was so paraphasic as to be practically incoherent. As it had been impossible to collect urine owing to her incontinence she was weighed and found to have lost 6 lb. (2.7 kg.) between 11 a.m. and 6 p.m. on Sunday. By Monday morning she had recovered completely, seeming rather smug and pleased with herself for having presented us with such a lovely experiment. A blood sample taken on Monday morning indicated that there was some haemoconcentration (Hb=116%, P.C.V.=51%). In this connexion it should be mentioned that the patient had been given no fluids through the whole length of the episode. There were, however, no symptoms of salt depletion nor any evidence of haemolysis.

The lesson to be learnt from this little incident would appear to be that water intoxication can produce a rather alarming clinical picture, but that full recovery without residual damage occurs. Treatment is simply that of the unconscious patient in status epilepticus. This rather unusual complaint receives scant mention in the literature and it would be interesting to hear of similar cases.—I am, etc.,

St. John's Hospital, Stone, Bucks. R. EMERY.

Topical Triamcinolone

SIR, — Triamcinolone, the 9-alpha-fluoro-16-alpha hydroxy derivative of prednisolone, is a new improved corticosteroid, alleged to have an anti-inflammatory effect 40 times as great in animals as cortisone or hydrocortisone. It has recently been put on the market as

"adcortyl-A ointment," consisting of triamcinolone acetonide 0.1% in plastibase.

No report of its topical use has appeared up to date in this country, and this letter is to report on a preliminary evaluation of this highly active steroid, following on the lines as suggested by Professor J. W. Crofton in his address on controls at the Symposium on Clinical Trials held at the Royal Society of Medicine (see *Journal*, May 3, 1958, p. 1056), using for the control group one of the best local treatments recognized—namely, hydrocortisone ointment. Symmetrical eruptions were selected; there was no blind trial, the hydrocortisone ointment used being one of the recognized proprietary brands, and sometimes our own preparation as prepared by the hospital pharmacist. Patients were treated for periods of one week to one month. Results to hand are as follows:

Triamcinolone Acetonide (0.1%) *Compared with Hydrocortisone Ointment* (1%)

	Triamcinolone Better Than Hydrocortisone	Hydrocortisone Better Than Triamcinolone	Failed to Respond
Flexural eczema ..	18	13	3
Atopic dermatitis ..	12	10	—
Contact dermatitis ..	9	3	—
Neurodermatitis ..	11	9	3
Pruritus ani	12	3	5

In 62 out of 111 cases, 0.1% triamcinolone acetonide was more effective. Without being over-optimistic, here is a new corticosteroid which promises to be even more valuable for topical use than hydrocortisone. I should be interested to know if anyone else has carried out such a trial.

My thanks are due to Messrs. E. R. Squibb for supplies of adcortyl-A ointment.

—I am, etc.,

Hove, 2, Sussex. E. COLIN-JONES.

Telling the Cancer Patient

SIR,—There is some disagreement on this, arising out of failure to recognize that there are two separate problems to be dealt with at the same time, and these must be diagnosed separately.

To the doctor "cancer" is an imprecise word, suggesting adenosarcoma, or squamous-celled carcinoma, or what not, giving no indication as to distribution or rapidity of spread. To the patient what does "cancer" mean? It is an imprecise word suggesting unspeakable dissolutions, agonies, and faceless horrors.

Should we tell the cancer patient? We cannot tell him anything truthful unless we speak the same language. Occasionally the patient will ask the direct question: Is it cancer? Answer truthfully the underlying question, and the direct question will be allowed to lapse. To patient A this symptom is a warning that the time is coming to put one's affairs in order. He is directed to a forward-looking and constructive task, and away from morbid fears. To patient B: You have no pains or agonies, you are as well after the consultation as before, nothing at all has happened. We have a task for the future. We, the patient and doctors, will deal with the present situation now, and any changes later. The patient is brought into the team and given the protection he needs.

Neither A nor B wished to be told he had cancer. Each has now the support he needs, and will co-operate fully with the actual treatment of the malignant condition. In cancer there are two conditions to be treated separately—the malignant growth, and the patients' mental, psychological, and/or spiritual reaction.

The question of educating the public about cancer is very different, but both these separate aspects should be kept in mind.—I am, etc.,

Crowthorne, Berks. H. D. FORBES FRASER.

Anaesthesia for Bronchoscopy

SIR,—There has been a marked tendency in recent years to change from local to general anaesthesia for bronchoscopy. I agree that this is preferable when bronchoscoping patients up to the age of about 40 years who have a full set of teeth. However, I still perform the majority of bronchoscopies on middle-aged and elderly patients under local anaesthesia, and I believe it has certain advantages.

It largely eliminates the troublesome coughing which can follow bronchoscopy under general anaesthesia and also the need for extra nursing staff to look after the patients who may be slow to recover consciousness. This applies to a session lasting an hour, during which six to eight patients are bronchoscoped under local anaesthesia. Bronchoscopy in an edentulous patient under local anaesthesia causes very little disturbance provided adequate pre-operative sedation is given and the mouth and larynx are expertly anaesthetized.

For a period of four years I used 2% amethocaine as the local anaesthetic agent, and during this time only one severe sensitivity reaction occurred. The case was one of five recently reported by Dr. S. K. Gupta (*Journal*, March 14, p. 695). Since then I have used 4% lignocaine and have found it entirely satisfactory.

I have always felt that the most uncomfortable part of the local anaesthetic is the application of laryngeal brushes to the pyriform fossae, and therefore during the last year I have replaced this part of the procedure by an aerosol of "nestosyl" oily solution which contains benzocaine and butylaminobenzoate; this is a quick and effective method of anaesthetizing the larynx, and I have used it in conjunction with an endotracheal injection of 2 ml. 4% lignocaine. All patients are premedicated an hour beforehand with 25 mg. chlorpromazine, 50–100 mg. pethidine, and 1/100 gr. (0.65 mg.) atropine. On the way to the theatre a 1-gr. (65-mg.) amethocaine lozenge is sucked. The aerosol is sprayed through a long, fine, curved nozzle over the back of the tongue, directing the spray towards each pyriform fossa for five seconds. This technique has been used in the last 350 patients for bronchoscopy with no sensitivity reactions. A similar technique has been used when anaesthetizing patients for bronchography.

—I am, etc.,

Department of Thoracic Surgery, North Middlesex Hospital, London, N.18. MICHAEL BATES.

Glucose-tolerance Tests

SIR,—The recent annotation on glucose-tolerance tests (*Journal*, May 23, p. 1340), which deals mainly with the interpretation of equivocal test results, concludes that "there is a need for a simple standardized technique which would be acceptable to all workers in the field." It seems to me that the rapid intravenous test as described by Ikkos and Luft[1] has much to recommend it, not only because of its simplicity but mainly since it provides a satisfactory numerical index of glucose utilization. Basically the test entails the intravenous injection of 50 ml. 50% dextrose within two to three minutes during the fasting state, and estimating the

glucose content of two blood samples, one taken 25 minutes after injection and the other after a further carefully timed interval of, say, 20 minutes. It is based on the observation that when injected glucose has diffused uniformly throughout the extracellular space (a process which takes 25 minutes with a 25-g. glucose load), blood glucose concentration is thereafter an exponential function of time. Consequently, when the logarithm of blood glucose concentration is plotted against time a straight line is obtained, from the slope of which the rate of removal of glucose from the blood is readily calculated. There is evidence which suggests that this index of glucose utilization is a constant for the subject tested.[2,3]

A wider use of this index would, I submit, provide data on the distribution of glucose utilization rates in the normal population which would allow a more accurate assessment of abnormality than is at present possible. Thus, knowledge of the mean value and standard deviation for an age group would be particularly useful in the interpretation of low individual values, and it might be found, for instance, that there is a zone between the lower limit of normality and the higher limit of diabetes where values given by potential diabetes occur. In any event, this numerical index would lend itself particularly well to the serial testing which would clarify such problems.—I am, etc.,

Goodmayes Hospital, Essex. IVOR G. PRYCE.

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Breast Abscess

SIR,—In their letter (*Journal*, June 20, p. 1588) Mr. D. H. K. Soltau and Mr. G. W. Hatcher seek information about the prevention of colonization of new-born babies by antibiotic-resistant staphylococci.

An outbreak of staphylococcal infection associated with one maternity department of 41 beds with some 40 cases of breast abscess, the majority due to penicillin- and tetracycline-resistant *Staph. pyogenes* phage type 81, was rapidly brought under control by the following means. (1) Bacteriological examination of mothers, babies, staff, and environment. (2) Treatment of one carrier found amongst the staff. (3) Spring-cleaning of the department and attention to detail of aseptic and antiseptic measures. (4) Cessation of routine bathing of babies. (5) A five-day course of erythromycin given to all mothers and babies. (6) A follow-up letter sent on discharge of each patient to their general practitioner requesting information about any subsequent sepsis.

From our investigations we concluded, as others have done, that the primary factor causing the outbreak was the very high (81%) carriage rate of the epidemic strain of staphylococcus amongst the normal babies in the unit. In an attempt to prevent the recurrence of this situation we have since examined nose and umbilical swabs as a routine from all babies immediately prior to discharge. This showed first a period of 17 weeks with only an occasional resistant strain (not type 81) found, though a fairly constant high proportion of babies had acquired sensitive strains, presumably from their mothers. Second, over the next six weeks a gradually increasing incidence of resistant strains of a variant of phage type, with no abnormal incidence of breast abscesses. Third, an increasing colonization of babies by a resistant phage type 80 strain reaching 85% of all infants in seven weeks. At this time we predicted that an increased incidence of breast abscesses would occur. In fact this did take place in due course (nine cases being discovered as well as 15 cases of other type 80 infections relating to this period).

To prevent an extension of this second outbreak of infection the following further steps were taken. (1) A weekly review of the situation was made by the medical and nursing staff concerned. (2) Bacteriological survey was repeated. (3) Treatment of one carrier and one case of infection discovered amongst staff. (4) Spring-cleaning of the department was repeated. (5) Dusting powder containing hexachlorophane was used on babies. (6) Neomycin drops were applied to babies' noses after every feed whilst in hospital (see below). No further breast abscesses have been reported in patients delivered after this time. As expected, the neomycin treatment caused virtual elimination of nasal staphylococci, the umbilical carriage rate being similarly affected.

After five weeks nasal drops were discontinued, but resistant *Staph. pyogenes* phage type 80 returned during the next two weeks in increasing numbers in the routine discharge swabs. Fearing the occurrence of further breast abscesses, nasal drops were reintroduced for a further six weeks, with the expected prompt suppression of carriage of all staphylococci. Again after discontinuing the nasal drops *Staph. pyogenes* phage type 80 has been found in the nose of one baby. This is the present position.

We think that our experiences show the value of routine swabbing of nose and umbilicus from all babies discharged from maternity units. Developing "epidemic" situations may then be detected early enough to take preventive measures. We have found that the instillation after every feed, into each nostril of all babies, of one drop of 0.5% neomycin sulphate in isotonic neutral solution has resulted in the total suppression of staphylococci in this situation, though this change is not wholly reflected in the babies' environment. We have had no reports of breast abscesses relating to periods when such measures were being taken or evidence of any untoward effect on the infants.—We are, etc.,

W. H. J. BAKER.
D. R. CHRISTIE.
County Hospital, Hereford.

Chemotherapy in Tuberculosis

SIR,—It is a great pity that in his capital survey of chemotherapy in tuberculosis Professor John Crofton (*Journal*, June 27, p. 1610) quotes the old canard that the report of the Medical Research Council[1] proved that when P.A.S. is combined with daily streptomycin "the dose of sodium P.A.S. must be 20 g. daily if drug resistance is to be prevented." The report did nothing of the kind. It showed that 5 g. P.A.S. four times daily was better than 2.5 g. four times daily, and no one has ever tried to show whether four doses of 5 g. P.A.S. are better than two or three doses of 5 g. in this combination. In a later report[2] it was shown that, when given in combination with isoniazid, 5 g. P.A.S. twice daily gave as good results over the trial period as 5 g. four times daily, and, though this finding is not strictly relevant, it is worth bearing in mind.

Reiteration of the statement that 20 g. is necessary had the unfortunate effect that, in the face of intolerance, doctors were inclined to diminish the dose rather than the number of times it was given, and regimes of 4 g. or even 3 g. four times daily came into use. Almost certainly 5 g. three times daily would have been better, and it is high time that 5 g. P.A.S. should be accepted

as the standard individual dose in combination with streptomycin as it is with isoniazid.

I do not wish particularly to advocate the use of P.A.S. in any combination, for it has been shown to be less good than regimes including isoniazid and should rate as second-best treatment. I wish only to draw attention to the facts, for, as is well known in the North, "facts are chiels that winna ding."—I am, etc.,

St. Wulstan's Hospital, Malvern. T. W. LLOYD.

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[2] —— ibid., 1955, **1**, 435.

Chlorpromazine in Tetanus

SIR,—I wish to draw your attention to a mistake which appeared in the paper by J. R. Lawrence and M. J. W. Sando (*Journal*, August 1, p. 113) in quoting from Laurence *et al.*[1] concerning the dose of chlorpromazine given in tetanus. The dose given was 500 mg. intravenously and not 50 mg. as stated. In this particular patient an abscess which had not appeared obvious during the acute stage of the illness was found at necropsy in the soft tissues of one foot. Toxin was obviously being elaborated from this abscess and influenced the enormous dose of chlorpromazine. However, I should like to add that, as stated in a more recent paper,[2] a dose of 50 mg. of chlorpromazine intramuscularly four-hourly in combination with 200 mg. of phenobarbitone sodium given as required achieved satisfactory control of spasms in all the cases, including the most severe ones. Only 3 patients out of 27, of whom 16 were regarded as severe, required more than 1.0 g. of phenobarbitone sodium in addition to 300 mg. chlorpromazine in any one day, and even their spasms were adequately controlled with slightly larger doses of phenobarbitone sodium.—I am, etc.,

London, N.15. E. BERMAN.

REFERENCES

[1] Laurence, D. R., Berman, E., Scragg, J. N., and Adams, E. B., *Lancet*, 1958, **1**, 987.
[2] Adams, E. B., Wright, R., Berman, E., and Laurence, D. R., ibid., 1959, **1**, 755.

*** A correction appears at p. 200.—ED., *B.M.J.*

The Kinins

SIR,—Your article "Keeping up with the Kinins" (*Journal*, July 25, p. 95) contains some inaccurate statements to which I would like to draw your attention.

(1) Rocha e Silva introduced the term "bradykinin" to describe a polypeptide causing slow contraction of plain muscle which was formed by the action of the venom of the snake, *Bothrops jararaca*, on serum. When similarly acting polypeptides were obtained by other means it was felt necessary to introduce the more generic term "plasma kinin," since it was not certain whether the same active principle was present in each case.[1]

The term plasma kinin includes bradykinin as well as kallidin, pain-producing substance, and other unnamed bradykinin-like substances. All these active polypeptides are formed from plasma in different ways, but they are indistinguishable when tested biologically, all causing a slow contraction of plain muscle and vasodilatation. It is possible that the same active principle is responsible for the activity of the different plasma kinins, and the biological evidence from parallel assays is in agreement with this hypothesis. On the other hand, there is no proof of this yet. The question can be settled only by elucidation of the chemical structure of the isolated peptides.

(2) In view of this it is not justified to say, "To-day we know that bradykinin and kallidin are the same substance . . . ," for the chemical structure of these substances is still unknown.

(3) The statement "another kinin is plasma kinin" is also incorrect, since plasma kinin is a generic term and does not refer specifically to the one formed by plasmin, as the article implied.

(4) Wasp kinin differs from the other kinins because it *is* destroyed by trypsin, not because it *is not* destroyed, as stated.

(5) The term "kinin" was originally used to describe the active peptide in wasp venom, but it is now used more widely to include the plasma kinins, urinary kinins, wasp kinin, and colostro-kinin. In the article the term is applied more generally to physiologically active polypeptides which have the common property of causing contraction of smooth muscle. Substance P, for example, is referred to as a kinin. Such wide application of the term kinin would mean that oxytocin, the vasopressins, the angiotensins (hypertensins), pepsitensin, and pepsitocin are also included. Since all these as well as substance P show definite differences in their biological properties from the kinins there seems little justification for such an extension of the term.

(6) Finally, it should be mentioned that the idea that functional hyperaemia in salivary glands was due to the release of a plasma kinin was put forward by Hilton and Lewis.[2 3] Their experiments were the first indication of the physiological role of these substances.—I am, etc.,

National Institute for Medical Research, London, N.W.7. E. W. HORTON.

REFERENCES

[1] Lewis, G. P., *J. Physiol. (Lond.)*, 1958, **140**, 285.
[2] Hilton, S. M., and Lewis, G. P., ibid., 1955, **129**, 253.
[3] —— —— ibid., 1956, **134**, 471.

St. Luke's Day Service

SIR,—May I, through the courtesy of your correspondence columns, once again draw the attention of your readers to our special service for doctors which is to be held in All Souls Church, Langham Place, W.1, this year on Sunday, October 18, at 11 a.m. ? We greatly value our link with the medical profession, and have been encouraged by the support which they have given to these services during the last seven years. Sir Geoffrey Marshall and the Minister of Health, Mr. D. Walker-Smith, M.P., have kindly agreed to read the lessons.

We shall be happy to reserve seats for doctors and members of their family who apply for tickets in advance. Application (stating the number of tickets required) should be made to the Church Secretary, All Souls, Langham Place, W.1, by October 15.—I am, etc.,

London, W.1. JOHN R. W. STOTT, Rector of All Souls, Langham Place.

Correction.—We much regret the mistakes in the letter from Dr. E. Eric Pochin on the subject of radioiodine in thyrotoxicosis (July 25, p. 97). First, the author's name was misspelt; secondly, the final sentence of the first paragraph should have read as follows: "The leukaemia was described as acute in nine of these cases and developed at about 18 months after radioiodine treatment in six of them, occurring after 2, 2½, 3, and 7 years in the remaining four"; and, thirdly, the volume and page number of the last reference (*New Engl. J. Med.*, 1959, **260**, 76) were misplaced.

Obituary

VLADIMIR KORENCHEVSKY, M.D.

Dr. V. Korenchevsky, formerly director of the Oxford Gerontological Research Unit, died suddenly in London on July 9, aged 79.

Vladimir Korenchevsky was born in Russia on January 15, 1880. He graduated in medicine from the Imperial Military Medical Academy at Petrograd in 1903, but as an undergraduate he had already published the results of some original research. He continued to work in the fields of physiology and pathology after graduation, and in 1908 engaged in research on gastro-intestinal auto-intoxication at the Pasteur Institute, Paris, in Professor I. Metchnikoff's department. In 1910 he proceeded to the degree of M.D. and continued his studies of the gastro-intestinal canal in Professor I. P. Pavlov's Institute of Experimental Medicine at Petrograd. When 32 years of age, in 1911, he became professor of experimental pathology in the Imperial Military Medical Academy. After the revolution he resisted the policy of the Soviet Government in the Academy and University, and was in danger of losing his life. In 1920, however, he was able to emigrate to England, and subsequently acquired British nationality.

For the next twenty-five years he worked in London as a senior research worker at the Lister Institute, being partly supported by a grant from the Medical Research Council. In 1945, with the aid of donations from Lord Nuffield, he established the Oxford Gerontological Research Unit, receiving much assistance from Professor E. G. T. Liddell in whose department of physiology the unit was housed. Six years ago Dr. Korenchevsky decided the time had come to assure the future of this unit, and by agreement with St. Bartholomew's Hospital medical school it was transferred to London to be incorporated in Professor K. I. Franklin's department of physiology. Here it was renamed "The Nuffield Gerontological Unit," and it continues to carry out the experimental gerontological research initiated at Oxford.

Dr. ELUNED WOODFORD-WILLIAMS writes: During his life Dr. Korenchevsky wrote at least 150 papers, and also had time and effort to stimulate the organization of gerontological societies in all European countries, the U.S.A., and the Argentine. In his travels for this purpose he was generously supported by grants from Lord Nuffield, and by Ciba Limited, through Dr. K. Miescher. Collaborating with Professor Brüll, he organized the first International Gerontological Congress in Liége in 1950 and at this congress stimulated the establishment of the International Association of Gerontology. For his work in this field he was made a permanent member of the governing body of this association. At the second International Congress of Gerontology, held in 1951 in St. Louis, he proposed the establishment of a special research section of the association. The idea was accepted and a special session on the lines suggested was held under the chairmanship of Dr. Korenchevsky and Dr. J. A. Huet. The success of this first session encouraged the organization by Professor Brüll, Sir Arthur Thomson, and Dr. Korenchevsky of the first conference of the European division of the research committee of the International Association of Gerontology in Liége in September, 1952. Thereafter Dr. Korenchevsky concentrated on summarizing his own work and the research of others on the physiology and pathology of ageing. These results he intended to publish in a book to be entitled "Physiology and Pathology of Ageing." The work was completed just before his death, but unfortunately he had no time to arrange its publication.

Dr. Korenchevsky faced opposition with courage and persistence, being convinced that ultimately his belief in the importance of gerontology would eventually be accepted. Many of his ideas have become realities; there are others which have yet to be fulfilled. One of these which he felt to be of particular importance was the establishment of a chair of gerontology in a British university. Not only was he undeterred by opposition, his rate of work was exceptionally fast throughout a long life, and the pace was maintained till the end. This quality of his, derived from an intensely logical intellect, was driven by a deep religious zeal for humanity, moderated by a sense of humour which was never far below the surface. He recreated his energy in his garden, and particularly in the support and comfort of his home, which was dear to him. His friends extend their deepest sympathy in their loss to his widow and his daughters, with whom he maintained close companionship through many years.

ARTHUR STEINDLER, M.D., Hon.F.R.C.S. F.A.C.S.

Dr. Arthur Steindler, emeritus professor of orthopaedic surgery at the State University of Iowa and an orthopaedic surgeon of international renown, died recently in Iowa City, aged 81.

Arthur Steindler was born in Vienna on June 22, 1878. He studied at Prague and Vienna, graduating M.D. in 1902. Five years later he emigrated to the United States, becoming an American citizen in 1914. He occupied the chair of orthopaedic surgery at Drake University, Des Moines, from 1910 to 1913, and the corresponding chair at the State University, Iowa City, from 1915 until 1949.

From his early days in the United States Dr. Steindler was known as a surgeon of great skill and deep learning. He devised several operations and was the author of a number of books, including *Reconstructive Surgery of the Upper Extremity* (1923), *Diseases and Deformities of the Spine and Thorax* (1929), *Orthopedic Operations* (1940), *Postgraduate Lectures on Orthopedic Diagnosis and Indications* (four vols., 1950–2), and *Kinesiology of the Human Body* (1955). Honoured by surgical societies all over the world, he was admitted an honorary Fellow of the Royal College of Surgeons of England in 1954. He was also an honorary Fellow of the Royal Society of Medicine.

We are indebted to Mr. H. J. SEDDON for the following appreciation: Arthur Steindler was the encyclopaedist of orthopaedics. His insatiable curiosity, knowledge of languages, and avidity as a reader gave him a width of knowledge which has perhaps never been equalled. When he was well over 70 he could be seen at a clinical meeting examining one patient after another and making notes about all he saw and heard. Up to the last year of his life he continued to write and to circulate his remarkable seminar notes, a collection of thoughtful essays on a great variety of topics. It would have been pardonable if, with all this learning, he had not been inventive. Yet he was a great pioneer, as is well shown by his books on the mechanics of the body and by the very original and simple operations he devised, operations based on a shrewd appreciation of the nature of the deformity or paralysis he was seeking to remedy. I have never met a man who combined more learning with so much practical ability.

Yet with all this there was nothing forbidding about him. He was almost shy, friendly when the ice was broken, and astonishingly humble. He was incapable of any kind of artifice and was transparently honest. If he disagreed with someone there was no nonsense about it: he said what he thought. But he dealt very tenderly with younger men and was generous in his appreciation of their work. So it was not surprising that Iowa city became a great centre that attracted pupils from all over the world, and when I first went to the United States nearly 30 years ago I came across surgeons who proudly described themselves as Steindler men; when I went to Iowa I found out why.

He cared nothing about social graces. The charm of his company came from his openness, his kindliness, and his enthusiasm. I never knew much about him apart from work, except in one respect—his passion for music. I remember once, in his home, his dashing through several

Bach duets with fiery ardour, keeping time with a one-two-three-four that was well above a whisper. On another occasion, many years later, I found him moved almost to tears at the end of a little recital. I believe that after a long day Steindler sometimes used to read a score in bed; the music composed him to sleep.

A curious feature of this great man was that he did not express himself easily. His writings tended to be heavy, and as a lecturer he was not always easy to follow. But because he had so much to give we listened to him with the most earnest attention and even ploughed through his ponderous books. At the bedside or in an out-patient clinic it was different. He listened to the story, looked at the patient, grasped everything, and then followed a lively and sometimes brilliant discussion. That was when he was at his best as a teacher.

Steindler was one of those rare men who never grew old. The freshness of his mind, his lovableness, and his enthusiasm will be remembered by his friends and pupils, and his influence on orthopaedics is imperishable.

S. M. WELLS, M.D., F.R.C.S.Ed., F.A.C.S.

Dr. S. M. Wells, who was in general practice at Valparaiso, Chile, for many years, died at his home there on May 11.

Stanley Martin Wells was born at Lima, Peru, in 1882. He came to England in 1897 to complete his education at Forest School and Guy's Hospital. After qualifying in 1905 he held the appointments of house-surgeon at Guy's Hospital, senior clinical assistant at the Rotunda Hospital, Dublin, and house-surgeon at the Lewisham Hospital. Admitted F.R.C.S.Ed. in 1907, he took the L.M. at the Rotunda Hospital in the same year. He then returned to South America, first to Lima, where he practised for a time before settling in Valparaiso. In order to practise in Peru and Chile he had to obtain, first, the degree of M.D. of Lima University, which he did in 1908, and of Santiago University, which he took in 1909; he also had to pass examinations in the Spanish language. At Valparaiso, where he was the leading British medical practitioner, he was for a time visiting surgeon in charge of the British and American Hospital there, and for many years he was on the honorary staff of the Children's Hospital, being chiefly interested in diseases of children and in obstetrics. In 1925 he was elected a Fellow of the American College of Surgeons. He leaves a widow, formerly Miss Ethel Rowe, and a married daughter, who lives in London.

BERNARD HAIGH, M.B., B.Chir.

Dr. Bernard Haigh, the senior among the general practitioners in Worthing, died on June 18, aged 80.

Bernard Haigh was born on September 4, 1878, the son of Canon Henry Haigh, archdeacon of the Isle of Wight. From Lancing College he entered Caius College, Cambridge, and from there went on to St. Bartholomew's Hospital. While still a student he had joined the Cambridge University volunteer company of the Royal Suffolk Regiment, and saw service as a combatant in the war in South Africa in 1900–1. Qualifying in 1908, he later graduated M.B., B.Chir. Dr. Haigh had seen much medical service abroad. He served with the Red Crescent in the Turco-Italian war of 1911–13, after which he was medical officer to an East African survey expedition. Having gone out to Malaya in 1914, he returned to England in 1916 to join the R.A.M.C. and then served in Mesopotamia and Palestine during the first world war. After the war he joined the late Dr. Frank Hinds in practice at Worthing, where he was also honorary medical officer to the local hospital until 1946. He married in 1914 the daughter of the Rev. W. M. Furneaux, dean of Winchester.

J. G. J. G. writes: Dr. Bernard Haigh was a greatly respected practitioner, and in his practice the doctor–patient relationship was ideal. Losing him, his patients have lost a true friend, one who in the work he loved had striven for their welfare with selfless devotion. He struggled against a progressive wasting condition of muscle for some two years, this compelling his retirement last autumn. When work had to be abandoned, he faced the inevitable downhill journey with the courage to endure.

LADY EWING, O.B.E., M.Sc., LL.D., D.C.L.

Lady Ewing, an international authority on the education of deaf children and wife of Sir Alexander Ewing, professor of education of the deaf in the University of Manchester, died in Manchester on July 16.

J. L. B. writes: Lady Ewing was an outstanding name throughout the world in the education of deaf children. She overcame her own handicap of otosclerosis as well as of increasing ill-health, and her work, together with that of her devoted husband, who contributed much from the scientific side in a most effective partnership, transformed the outlook for the deaf child. Her intuitive understanding and her ability to assess all the many factors concerned in deaf children helped her to give confidence, inspiration, and skilled help to parents.

Lady Ewing and her husband published many books and papers on the education of the handicapped. In 1943 they shared the Norman Gamble prize of the Royal Society of Medicine and in 1942 the Actonian prize of the Royal Institution. They both became honorary members of the American Otological Society in 1946. Between 1946 and 1950 they visited schools in Australia, Canada, and New Zealand to advise on the provision of education for the deaf, and conducted postgraduate courses during a summer session at the Northwestern University, Illinois.

As Miss Irene Goldsack, and later as Mrs. Ewing, she was responsible for the establishment of the department of the education of the deaf at Manchester University shortly after the first world war. Fortunately, when her husband and former pupil succeeded her as Ellis Llwyd Jones professor of the education of the deaf at Manchester University, she found time to write several books, among them *Speech and Deaf Children* and *New Opportunities for Deaf Children*, which contain some of her teaching but scarcely indicate the magnitude of her contribution to research, or her psychological insight into the child and his parents, or her pioneering spirit. Throughout her work she co-operated closely with otologists and doctors in general practice and in the public health service.

Sir HUGH DEVINE, M.S., Hon.F.R.C.S. F.R.A.C.S., F.A.C.S.

Sir Hugh Devine, formerly senior surgeon and dean of St. Vincent's Hospital Clinical School, Melbourne, and a past-president of the Royal Australasian College of Surgeons, died at Melbourne on July 18. He was 81 years of age.

Hugh Berchmans Devine was born on May 13, 1878, and was educated at St. Patrick's College, Ballarat, and at Queen's College, Melbourne. He graduated M.B., B.S., with first-class honours in medicine, from Melbourne University in 1907, and proceeded to the M.S. in 1914. During the first world war he served as a lieutenant-colonel in the A.A.M.C. In 1926, with Sir George Syme and R. Hamilton Russell, he took the first step towards the foundation of the Royal Australasian College of Surgeons, and later in the same year was appointed a member of the provisional executive committee which drew up the constitution of the College, and in 1927 he was elected to the first council, on which he served for many years. Elected a vice-president of the College in 1933, he was president from 1939 to 1941. In 1939 he was elected an honorary Fellow of the Royal College of Surgeons of England, and a year or two before this he had been similarly honoured by the American College of Surgeons. He was also an honorary Fellow of the Royal Society of Medicine and of the Association of Surgeons of Great Britain and Ireland. He was knighted in 1936. The author of *The Surgery of the Alimentary Tract*, published

in 1940, he also wrote, in collaboration with his son, Mr. John Devine—himself an eminent surgeon—a textbook entitled *The Surgery of the Colon and Rectum.*

In 1912 he married Miss Mary O'Donnell, by whom he had one son and two daughters.

We are indebted to Sir GORDON GORDON-TAYLOR for the following appreciation: Perhaps the courtesy of a few lines of the *Journal* might be vouchsafed me to pay a tribute to a great Melbourne surgeon, who was not only my loyal friend of many years but also a colleague, for St. Vincent's Hospital honoured me by electing me a member of their consultant staff some years ago. Sir Hugh Devine had attained the age of 81, and throughout his long life he had two outstanding loyalties—the Royal Australasian College of Surgeons and St. Vincent's Hospital.

He was proud of the important part he had played in the creation of the Australasian College, of which he was destined to become president. During his almost lifelong connexion with St. Vincent's Hospital Devine had many distinguished surgical colleagues: Sir Thomas Dunhill, Sir John Newman-Morris, and Julian Smith, sen., are notable names, but Dunhill came to Britain and St. Bartholomew's soon after the termination of the 1914–18 war; Newman-Morris's rare gifts were sublimated to devoted service to the Australian Red Cross, involving more than one mission during the war years to Britain and America; and Julian Smith's repute as a surgeon is apt to be forgotten when his skill as one of the supreme amateur photographers of all time is borne in mind, while his genius in devising and fashioning multitudinous and multifarious surgical instruments of great value is sometimes remembered to the detriment of his one-time fame as a surgical operator. The very mention of "St. Vincent's" automatically conjured up the name of Devine, who remained its loyal and devoted servant for nearly half a century. He was essentially a surgical artist, bent on improving his art and promoting the safety of surgery.

As surgeon to an institution which Dunhill had made the cradle of the toxic goitre surgery of the world, Devine was skilled in the craftsmanship of thyroid surgery, but his international reputation rests largely on his contribution to the advancement of abdominal surgery, especially that of the colon and rectum. Doubtless antibiotics have outmoded some of the techniques which Devine championed, but they played a salutary role in the evolution of safe surgery for diseases of the large intestine, and thousands of lives must have been preserved by the employment of the method which he inculcated in contemporary operators.

His knife was always more skilful than his pen, and he lacked the gift of words possessed by his great friend, the silver-tongued Alan Newton. He was possessed of considerable business instincts, and these he employed to the advantage of the *Australian and New Zealand Journal of Surgery*, of whose editorial committee he was chairman for many years. His devotion to his wife, who suffered for many years from a distressing malady of the nervous system, commanded the admiration and affection of all privileged to enter their home. He suffered many blows from fate, but his religious faith enabled him to "bear his head right high." His contemporaries and pupils sought to show their regard and devotion towards him by dedicating a special number of the *Australian and New Zealand Journal of Surgery* to him on his eighty-first birthday. Doubtless some glimmering of this reached his ears and must have gladdened his heart, even if he may not have been privileged to read its list of contributors and the contents. Australia, and especially Victoria, will be the poorer for the loss of the famous old surgeon. It was good to have known and to count oneself a friend of "Hughie" Devine.

LADISLAV HARTMAN, M.D.

Dr. Ladislav Hartman, formerly a major in the R.A.M.C., died in Prague on July 9 at the age of 52.

A. B. writes: Born in Kosice, in Czechoslovakia, Ladislav Hartman graduated in medicine at Prague University and finally returned as a medical consultant to his home town. In 1939 he joined the Czechoslovak forces in the Middle East, and shortly afterwards was transferred to the R.A.M.C., serving with the Eighth Army. For a time he was both medical and education officer, an arduous and unusual combination of duties in which he was outstandingly successful. He was always popular with his fellow officers, and this was for him a very happy period of his life. At the end of the war he returned to Czechoslovakia, but was arrested in 1949 and sentenced to imprisonment for ten years on political charges. He was released before serving the full sentence, and permitted to work as a labourer in the uranium mines of Jáchymov. He died of carcinoma of lung.

Medical Notes in Parliament

MENTAL HEALTH ACT REACHES THE STATUTE BOOK

Parliament has risen for the summer recess, and there is a general expectation that it will meet again only to be dissolved for a general election about the end of October. Members have separated with the knowledge that the Government's programme for the session has been virtually completed. Prominent in any retrospect of that programme must be the passing of the Mental Health Act, which received the Royal Assent on July 29.

The argument whether there should be some lay representation in the decisions on detention remains unresolved, and on this the Bill stays unaltered.

In Clause 4, setting out the definitions and classification of mental disorders, two changes of substance were made. The first adds to the meaning of "severe subnormality" the phrase that the patient should not only be incapable of leading an independent life but should also be incapable "of guarding himself against serious exploitation." The purpose here is to make clear that the more severely retarded of patients now classified as feeble-minded are intended to fall into the severely subnormal category.

The second is the result of an effort by the Lords to improve the definition of the psychopath. It deletes from the original definition of psychopathic disorder as "a persistent disorder of personality" the last two words, and makes the definition now read "a persistent disorder or disability of mind."

The Minister of Health, proposing the amended version to the Commons, expressed the hope that it would go a long way to meeting the anxieties that had been expressed by members of the House. In this he had the concurrence of Mr. SOMERVILLE HASTINGS (Barking, Lab.) and Dr. DONALD JOHNSON (Carlisle, C.), but not that of Dr. EDITH SUMMERSKILL (Warrington, Lab.). She expressed serious misgivings about it, because many eminent psychiatrists believed that the psychopath was the product of his environment. The danger was that of affixing a label, which the experts had considered but rejected in the interests of the psychopath. Dr. JOHNSON had some reservations too about the looseness of definition about "mind" and the fact that the Bill seemed to leave the medical profession *carte blanche* to define what they meant by "mind" and "mental illness." Mr. HASTINGS accepted the amendment as a definite improvement, but did not think they had yet heard the last word on the definition of psychopath or psychopathic disorder. The MINISTER agreed.

DRUG COSTS CONTROL

On July 15 Dr. SUMMERSKILL demanded to know why, among other things, there had been no statement about the Hinchliffe report. The implementation of the Hinchliffe Committee's recommendations on the cost of prescribing she regarded as extremely urgent—in particular, the recommendation that a permanent expert body should advise the Minister expeditiously on all matters affecting the trend of costs in the pharmaceutical service. She said prescription

charges should be abolished, and called in aid both the Hinchliffe report and the B.M.A. She also promised that this was one of the first things the next Labour Government would do.

She wanted to know whether the Minister had agreed that free drugs could be supplied to private patients under the Health Service, and quoted a report in the *Journal* of April 11 (*Supplement*, p. 150) that agreement had been reached that a scheme for the supply to private patients on Form E.C.10 was administratively possible, and that the Minister had agreed to meet representatives of the Council immediately after the final Hinchliffe report.

Mr. D. WALKER-SMITH replied that the 11 recommendations in the Hinchliffe report dealing with medical training had been taken up with the medical schools. The trial recommendations were about to be discussed with the Royal Colleges; and the drug recommendations with the industry. The Ministry was having consultations with the B.M.A. and the College of General Practitioners on the recommendations for the voluntary limitation of drugs. On prescription charges, the Hinchliffe Committee had recommended that agreement be sought with the medical profession to limit the amount supplied on one prescription to that required for one week or less (with exceptions for chronic or special cases), and a trial period of two years for such a scheme. The Government regarded this as a constructive approach. If such a scheme could be set up, and proved successful in controlling expenditure on drugs, they would consider whether the saving justified the abolition of the prescription charge at the end of the two-year period, in the context of the finances of the Health Service and other relevant circumstances. Challenged specifically on the proposal for a permanent expert body of advisers on the pharmaceutical services, he stated that it was an interesting proposal that he was ready to consider further in the light of the reactions of the professional bodies and others who were being consulted.

Finally Dr. SUMMERSKILL sharply demanded an answer to her question about free medicine, which she said was fundamental to the Health Service. Mr. WALKER-SMITH told her he had met the representatives of the B.M.A. at their request. He would consider all they had to say, but he had not given them any promise.

QUESTIONS IN THE COMMONS

Registration of Medical Auxiliaries

Mr. J. A. KERSHAW (Stroud, Con.) asked the Minister of Health on July 28 whether he was now in a position to make a statement about the statutory registration of medical auxiliaries. In a written reply Mr. D. WALKER SMITH said: "Yes. The Government have considered a scheme for statutory registration worked out with the representatives of the medical auxiliaries concerned, the views of the medical profession on that scheme, and the comments of the professional bodies on those views, and have decided to introduce legislation at an early opportunity."

Future of Special Hospitals

On July 30 Mr. KENNETH ROBINSON (St. Pancras, N., Lab.) asked the Minister if he would announce the membership and terms of reference of the Working Party on the Special Hospitals at Broadmoor, Rampton, and Moss Side. Mr. WALKER SMITH replied that the terms of reference of the working party were: To consider the role of the special hospitals and the classes of patients to be treated in them, having regard to the new mental health law and to the provision to be made by the hospital service generally. The membership (apart from one invitation not yet answered owing to absence abroad) was to be as follows: Mr. J. E. Pater (chairman), Mr. P. Benner, Dr. T. M. Cuthbert, Dr. J. Graham, Dr. J. D. Hill, Mr. L. R. Lorimer, Dr. J. S. Mackay, the Hon. W. S. Maclay, Miss J. J. Nunn, Mr. R. F. G. Ormrod, Dr. P. D. Scott, and Mr. G. G. Hulme (the secretary of the working party to whom anyone wishing to submit evidence should apply at the Ministry of Health, Savile Row, London, W.1).

Universities and Colleges

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At the quarterly comitia of the College held on January 29, with the President, Professor Robert Platt, in the chair, Dr. N. G. Harris was reappointed College representative on the National Association for Mental Health; Sir Samuel Bedson at the eleventh meeting of societies supporting the Conference on the Supply of Experimental Animals; Professor A. P. Thomson on the court of governors of Birmingham University; Dr. E. R. Boland, Dr. T. C. Hunt, and Dr. J. B. Harman on the Central Medical Recruitment Committee for 1959-60. Dr. H. J. Orr-Ewing was appointed as College representative on the court of governors of Bristol University and Dr. J. A. Scott to the Health Congress of the Royal Society of Health.

Licences

Licences to practise were conferred upon the following 131 candidates who have passed the final examination in medicine, surgery, and midwifery of the Conjoint Board and who have complied with the bylaws of the College:

Abigail E. E. Amua-Sekyi, M. A. McL. Bailey, R. B. Barnbrook, E. J. Barnett, P. J. Beale, L. J. Beilin, B. A. O. Binns, B. Bisseru, R. M. Bradfield, J. S. Brown, Doreen R. G. Browne, J. C. Bull, A. E. Bullock, Jill A. Bunton, Hazel M. Burtenshaw, W. G. Cheyne, Katharine L. Codd, Ann R. Coe, J. A. Corbett, H. S. Cormack, A. M. Cotton, Barbara A. Croft, E. G. L. Davies, T. T. Davies, R. de Alarcon, P. J. De Buse, Avery S. Denfield, H. Dexter, B. W. M. Dorran, D. L. Easty, D. O. Ekwulugo, E. U. Essien, Valerie J. Everett, Monica J. Falkner, S. E. Farraj, Shirley Fish, W. E. I. Forsythe-Jauch, A. L. Freeman, Louise Gallagher, Sheila M. Gorringe, T. R. Gould, A. E. Green, P. R. Grob, Anne A. N. Grubb, J. M. Gurney, H. Haberfeld, A. P. Hall, C. E. Harley, Rosemary Harms, J. Harrower, B. A. Hasenson, M. T. Haslam, Elizabeth A. Hills, H. B. Holden, J. G. Holmes-Smith, W. Holms, Rita J. Hornik, C. A. Ifeakandu, Gillian A. Jefferies, Ann P. John, D. W. McN. Johnson, D. G. H. Jones, Shirley P. Jones, A. Kasbarian, B. N. C. Kempton, R. L. King, F. W. Knox, S. N. I. Krishnaswamy, Jean M. Kubale, K. L. Lancer, D. W. Laurie, P. A. Lawrence, R. D. B. Leicester, P. K. Lewin, M. J. Lewis, T. P. Linehan, Tee Fun Loh, Cynthia Lucas, I. S. Macdonald, Hazel J. McFarlane, Anne M. MacGregor, C. McL. Maddox, Valerie Major, N. Malcolm, Ann C. Martindale, D. D. Mathews, R. W. May, H. J. Missen, B. D. G. Morgan, P. A. Morris, M. K. Murphy, T. G. Nash, Ruth Ogden, Bak Chua Oh, T. C. Okeahialam, T. A. Oleghe, J. T. Outred, Ann Parry-Williams, R. Paul, D. K. Payler, P. E. Pearce, W. B. Pearce, M. G. Peters, Audrey E. Pett, A. D. Piatkus, E. C. Pye, C. A. Ramsay, M. I. Reeve, Jennie Robertson, T. W. E. Robinson, M. D. Robson, J. W. Rollins, G. C. Rowe, Helen Rubens, S. S. Sanders, M. Sarner, Margaret L. Shaw, D. J. Smith, J. H. Sowray, A. J. Spicer, June M. Squire, M. I. L. Stolar, T. C. Taylor, I. R. Thomas, A. F. Tredre, A. Veijajiva, A. L. Whiteson, C. E. R. Winer, J. Wolfe, W. Yen, June R. Zagni.

Diplomas

Diplomas in Laryngology and Otology, in Anaesthetics, in Medical Radiodiagnosis, in Psychological Medicine, in Pathology, in Public Health, and in Child Health were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of February 7 (p. 379). Other diplomas were granted, jointly with the Royal College of Surgeons of England, as follows:

DIPLOMA IN INDUSTRIAL HEALTH.—A. J. Barwood, A. Bhoomkar, J. L. Blonstein, T. N. N. Brennan, D. C. Curtin, B. R. Ellis, J. G. Jeffs, D. L. MacKinnon, S. Ray, T. H. Redfern, Z. Q. Shaikh, J. J. Slome, L. S. Sodhy.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—K. K. Appaji, G. Gajre, M. A. J. Khan, D. H. Melville-Swarries, Hnin Yee.

DIPLOMA IN MEDICAL RADIOTHERAPY.—J. N. Godlee, and to the other successful candidates whose names were printed in the *Journal* of February 7 (p. 380).

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on February 12 with the President, Sir James Paterson Ross, in the chair, the Hallett Prize was awarded to Dr. G. R. Duncan (University of Otago) and also to Dr. H. L. Eaton (University of Ceylon). The Handcock Prize was awarded to J. C. Bull (Guy's Hospital Medical School). A Diploma of Fellowship was granted to A. O. Wilkey. Diplomas of Fellowship in the Faculty of Anaesthetists were granted as follows:

J. A. Blundell, H. N. Chambers, Sylvia I. Duckworth, K. G. Lupprian, A. R. Bollen, Dorothy A. Westcott, A. F. M. Little, M. D. A. Vickers, J. R. S. Hutchison, G. D. Allen, M. W. Glossop, S. M. Laird, J. T. Davidson, I. B. Denny, Nerida M. Dilworth, A. S. Manavalan, V. Stanhill, V. S. Padmanathan, Margaret E. Riddoch, S. S. Barker, D. Campbell, D. W. Eyre-Walker, Annie Mortell, G. M. J. White, T. Forrest, A. Gilston, P. J. Healy, D. M. McWilliams, J. S. Miller, J. S. Robinson, R. B. Roe, R. J. Sweeney, P. J. Verrill, Joan M. Byrne, Henrietta P. A. G. McNeil, M. W. Potts, S. A. Feldman.

A Diploma in Medical Radiotherapy was granted, jointly with the Royal College of Physicians of London, to J. N. Godlee, and in Tropical Medicine and Hygiene to M. A. J. Khan.

Diplomas in Industrial Health were granted, jointly with the Royal College of Physicians of London, to the successful candidates whose names are printed above in the report of the meeting of the Royal College of Physicians of London.

Vital Statistics

Week Ending August 1

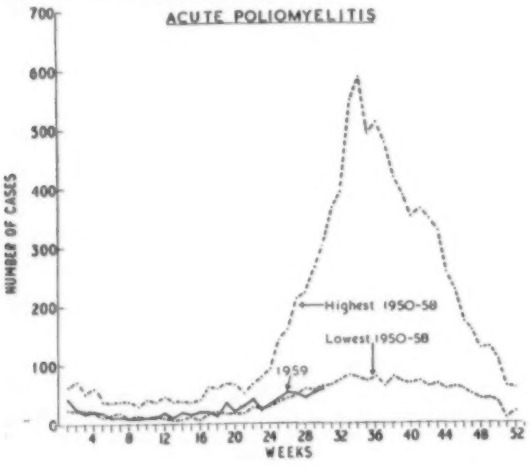
Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available:

	Week Ending July 25	Week Ending Aug. 1
Measles		
Isle of Ely	95	**114**
Whittlesey U.D.	28	**81**
Staffordshire	283	**356**
Stoke on Trent C.B.	34	**70**
Warwickshire	205	**213**
Birmingham C.B.	119	**119**
Dysentery		
London	57	**43**
Southwark	4	**13**
Staffordshire	43	**20**
Cannock U.D.	18	**11**
Bilston M.B.	13	**5**
Sussex	20	**14**
Brighton C.B.	19	**14**
Warwickshire	52	**52**
Birmingham C.B.	28	**36**
Coventry C.B.	17	**7**
Yorkshire East Riding	18	**10**
Haltemprice U.D.	11	**1**
Yorkshire West Riding	71	**68**
Todmorden M.B.	8	**15**
Acute Poliomyelitis		
London	12	**15**
Islington	6	**5**
Middlesex	6	**7**
Lancashire	5	**6**
Diphtheria		
London	1	**3**
Islington	0	**2**

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 25** (No. 29) and corresponding week 1958.

) Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	2	1		1		3	1	1	0	
Dysentery	596	57		4	5	712	105	122	4	1
Encephalitis, acute	0	0		0		1	0		0	
Enteric fever:										
Typhoid	5	1		0	10	4	1	1	1	
Paratyphoid	4	1		0		4	0	2(B)	0	5(B)
Food-poisoning	246	26		0		332	32	18	13	
Infective enteritis or diarrhoea under 2 years				18	20				13	18
Measles*	7,080	180		131	116	6,674	568	42	29	26
Meningococcal infection	21	1		1	2	15	0	12	0	1
Ophthalmia neonatorum	30	10		0		23	2	6	0	
Pneumonia†	168	5		4		220	16	97	3	1
Poliomyelitis, acute:										
Paralytic	35	6		1		37	3	21	3	7
Non-paralytic	18	7				20	1			
Puerperal fever§	221	53		0		223	46	10	0	
Scarlet fever	803	27		21	8	651	37	31	8	14
Tuberculosis:										
Respiratory	415	57		13		578	62	71	22	
Non-respiratory	69	8		0		81	9	14	6	
Whooping-cough	694	47		12	46	827	34	37	12	37

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0		0	0	1	0	0	0	0
Dysentery	3	0		0		1	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0	0		0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	2	0		0	0	6	0	2	0	1
Influenza	1	0		0	0	3	0	1	0	0
Measles		0		0	0		0	0	0	0
Meningococcal infection		0		0			0	0		
Pneumonia	342	33		9	4	281	28	8	6	1
Poliomyelitis, acute	4	0		0	0	4	0		0	0
Scarlet fever		0		0	0		0	0	0	0
Tuberculosis:										
Respiratory	55	4		1	1	49	5	5	1	2
Non-respiratory		3		1	1		3	2	0	0
Whooping-cough	0	0		0	0	1	0	0	0	0
Deaths 0–1 year	293	29	22	5	8	253	31	21	3	8
Deaths (excluding stillbirths)	8,016	608	528	109	120	7,842	632	464	102	126
LIVE BIRTHS	14,379	1282	1010	257	416	13,732	1092	516	202	373
STILLBIRTHS	292	20	30			306	24	28		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Emergency Bed Service.—The Service came of age this year on June 21, and its twenty-first annual report points out some interesting contrasts between then and now. In its first year it handled 8,309 cases; in the year ending March 31, 1959, the number had risen to 63,807. In 1938 it was necessary to try one and a half hospitals to get a patient admitted; the present figure is about three, probably because the word "emergency" is now less rigidly interpreted. The Service successfully weathered a crisis in February precipitated by influenza and fog, but the report points out that a notable feature of the epidemic was the number of patients who were stated by their general practitioners not to be responding to antibiotics, and says that the proportion of such patients appears to be increasing. It also expresses concern over the percentage of patients who have to be admitted by appeal to medical referees. The figure, 11.6%, is lower than it was, but it still falls short of the Service's target of not more than 10% admitted in this way, and to some extent indicates a failure of co-operation on the part of those concerned. The report expresses itself forcibly over the fact that only slightly over one-third of the maternity cases handled by the E.B.S. are regarded as genuine emergencies, the rest being due to last-minute requests to find a bed for normal maternity cases. Last year, when the total number of maternity cases handled was 1,699, this situation was said to call for "urgent remedy." To-day, when the year's figures stand at 2,591, the report says the need for action is even more imperative.

The Fountain, and Queen Mary's Hospital, Carshalton.—About 120 mentally defective children from the Fountain Hospital, Tooting, will be accommodated in three villas at Queen Mary's Hospital as soon as the necessary adaptations can be made. This is the upshot of the South-West Metropolitan Regional Hospital Board's decision to accept the Minister of Health's plan to establish a comprehensive hospital there for both physically and mentally sick children. In a letter to the Board, the Minister, Mr. D. WALKER-SMITH, says that he is satisfied that a new reception unit, out-patient department, and teaching and research unit should be on the site of the present Fountain Hospital, but when they can be provided will depend on the freeing of a suitable site, planning progress, and cost. The Board is now arranging for the provision of a single hospital management committee for the two hospitals.

Plastic Surgery Congress.—The British Association of Plastic Surgeons held an international congress under the patronage of H.R.H. the Duke of Edinburgh at the Royal College of Surgeons, London, from July 12 to 17. At the opening ceremony delegates of 27 national associations of plastic surgeons were welcomed by Sir JOHN CHARLES, chief medical officer to the Ministry of Health, Sir JAMES PATERSON ROSS, P.R.C.S., and Mr. RAINSFORD MOWLEM, President of the Congress. The scientific programme included papers on cleft lip and palate and other congenital conditions, cancer of the face and neck, cosmetic surgery, hand injuries, and research subjects. A continuous film programme was also arranged covering these and other important topics. Some 550 plastic surgeons were present from all over the world, and, accompanied by their ladies, enjoyed a well-organized social programme.

"Current Medical Research."—The review articles and illustrations from the Medical Research Council's 1957–8 report have been reprinted as a separate booklet (*Current Medical Research*, H.M.S.O., price 3s. 6d. net), which will be on sale from August 17. There is a "policy" article on the Council's laboratories in West Africa, and 11 review articles which cover such subjects as malaria in the Gambia, trachoma, leprosy, cancer-producing viruses, and the rehabilitation of chronic schizophrenics.

Dr. Rae Gilchrist, P.R.C.P.(Ed.), was recently made an honorary fellow of the Royal Australasian College of Physicians at a ceremony in Adelaide.

Medical Directory, 1960.—Any doctor who has not received the annual schedule or who has mislaid it and would like a duplicate is asked to apply for one, sending his full name and year of qualification for identification, to the Editor, The Medical Directory, 104, Gloucester Place, London, W.1. The speedy return of all schedules would be appreciated.

COMING EVENTS

2nd World—4th European Aviation and Space Medicine Congress.—Rome, October 27–31. Summaries to be sent before August 31 to the Organizing Committee, 2/A Via Piero Gobetti, Rome.

International Congress of Cancer Cytology.—In September, Madrid. Details from Mrs. E. L. MASELLI, P.O.B. 633, Coral Gables, Florida, U.S.A.

Association Nationale des Médecins Cinéastes et des Cinéastes Scientifiques de France.—4th session of the International Permanent Medico-Surgical and Scientific Film Festival, November, Nouvelle Faculté de Médecine de Paris. Those wishing to show films should send them to the Secretary-General, 23, Boul. de Latour-Maubourg, Paris, 7, before September 5.

19th International Congress of Pharmaceutical Sciences.—September 6–9, Zurich. Details from Professor K. STEIGER, 25, Clausiusstrasse, Zurich, Switzerland.

Institute for Study and Treatment of Delinquency.—Summer School, "Crime and Punishment," at Florence Nightingale Hall, Nottingham University, September 14–19. Applications to Miss EVE SAVILLE, I.S.T.D., 8, Bourdon Street, Davies Street, London, W.1.

4th International Congress of International Cardio-vascular Society.—September 18–20, Munich. Details from Dr. H. HAIMOVICI, 715, Park Avenue, New York, 21, U.S.A.

4th Meeting of International Medical Days.—October 1–4, Palazzo della Gran Guardia, Piazza Bra, Verona. Details from Professor GIORGIO CEVOLOTTO, Istituti Ospitalieri di Verona, Via Bassino, Borgo Trento, Verona, Italy.

5th International Convention on Nutrition and Vital Substances.—October 7–11, Konstanz, Zurich. Details from 61, Bemeroder Strasse, Hannover-Kirchrode, Germany.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Barker.—On June 2, 1959, at St. Helier Hospital, Carshalton, Surrey, to Jane (formerly Homfray) and Dr. John Charles Barker, M.R.C.P., a son—Nigel Homfray.

Beven.—On June 23, 1959, at Queen Charlotte's Hospital, London, W., to Suzanne (formerly Hassan) and Geoffrey Beven, M.D., a son—Paul Geoffrey Hassan.

Cooper.—On June 29, 1959, at Royal Northern Hospital, London, to Margaret and Charles Foster Cooper, M.D., M.R.C.P., a daughter—Francesca.

Coote.—On June 16, 1959, at Paddington General Hospital, London, W., to Margaret, wife of Barry Desmond Coote, F.R.C.S., D.O., of Sydney, Australia, a daughter—Gillian.

Laurent.—On June 12, 1959, in London, to Patricia (formerly Monk), wife of Dr. L. P. E. Laurent, a daughter—Susan Janeen.

Owen.—On April 3, 1959, at University College Hospital, Ibadan, Nigeria, to Jacqueline, Dip.H.Ed., and John Owen, M.B., Ch.B., D.P.H., Dip.H.Ed., a son—Philip Selwyn.

MARRIAGES

Shortridge—Ridout.—On June 12, 1959, at Knaresborough, Yorkshire, Douglas Shortridge to Dorothy Mary Ridout, F.R.C.S., M.R.C.O.G.

DEATHS

Connolly.—On June 2, 1959, at Foxrock, Dublin, Patrick Joseph Connolly, L.R.C.P.&S.I., L.M., formerly of Kenton, Middlesex.

McDade.—On June 4, 1959, at Roselands, Broomfield, Chelmsford, Essex, Robert Sinclair Charles McDade, M.B., B.Chir., aged 54.

McIntyre.—On May 26, 1959, at Freshfields, Sandy Lane, Newcastle, Staffordshire, James McIntyre, M.B., B.Ch.

Solomon.—On June 1, 1959, at Addenbrooke's Hospital, Cambridge, Moses Solomon, L.M.S., aged 68.

Wells.—On May 11, 1959, at Valparaiso, Chile, Stanley Martin Wells, M.D., F.R.C.S.Ed., F.A.C.S.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Cholesterol in Liver

Q.—*Does liver contain more cholesterol than other tissue?*

A.—The liver does not contain more cholesterol than any other tissue. The normal concentration of sterols is 300 mg. per 100 g. wet weight and the kidney and spleen contain about the same amount. Whole skin also contains this concentration but much of it is in the epidermis, which has a concentration of 900 mg. The aorta contains from 300 mg. upwards, depending on the amount of atheroma. The highest normal concentration in the body is in the adrenals, which contain 10 g. per 100 g.; whole brain in the adult contains 1.9 g., and the pituitary and testes about 500 mg.

Vitamins for Deafness

Q.—*Is vitamin therapy of any use in improving auditory nerve deafness?*

A.—Preparations containing vitamin A with the various factors of the vitamin B complex and other preparations have been used extensively for deafness due to changes in the end organ or nerve of hearing. Some observers have claimed that vitamin A in large quantities does improve perceptive (nerve) deafness, and it has also been suggested that vitamin A may protect against the harmful factors of over-stimulation of hearing by noise. However, vitamin A and the vitamin B complex are not receiving the attention that they formerly did. It has been recently suggested,[1] however, that vitamin B_{12} may be more effective, and certainly the writer has on several occasions found that vitamin B_{12} by injection has been followed by a slight improvement in hearing in a small proportion of cases of perceptive deafness.

REFERENCE

[1] Beickert, P., *Arch. Ohr.-, Nas.-, u. Kehlk.-Heilk.*, 1955, **167**, 636.

A.T.S. in Prophylaxis

Q.—*Is A.T.S. of any value as a prophylactic measure when the potentially infected wound is two days' old when first seen?*

A.—Antitoxin is of value only if it can come in contact with the toxin before it becomes bound to body cells. It is impossible to say in any one case when this has occurred, but, if it is logical to give antitoxin in treatment after symptoms of tetanus have occurred, it is surely logical to give it as a prophylactic a day or two after injury.

Allergy to Cosmetics

Q.—*What treatment may be given to a patient who has developed an allergy to face powder and lipstick?*

A.—Treatment here lies in the removal of the cause, and sometimes nature is more attractive than art. There are so-called non-allergic cosmetics available which might solve this problem. Alternatively, patch-testing to a variety of powders and lipsticks might indicate preparations to which the patient is not allergic. If necessary, patch-testing to each ingredient of the powder and lipstick would disclose the particular cause of the allergy, and cosmetics omitting those ingredients might then be supplied by the firm.

Face powders do not usually present an insuperable problem, and in the last resort a good medicinal powder, such as "pulvogen," can be prescribed and tinted by the chemist (as with lycopodium). Lipsticks are more difficult, since eosin (or impurities in eosin) is the usual cause and is present in almost all lipsticks. The sensitization is also in part dependent upon the ease of penetration of the thinner epithelium of the lip. The use of an ordinary barrier cream to the lip before applying the lipstick is sometimes effective.

Stability of Cup Arthroplasty

Q.—*Are subsequent pregnancies likely to have an adverse effect on the operative results of a cup arthroplasty for osteoarthritic changes in the hip due to epiphysial dysplasia?*

A.—Once the cup arthroplasty has become well established there seems to be the likelihood of it being stable or even improving a little as the years go by. Pregnancy should not have an adverse effect.

Fat in Eating-chocolate

Q.—*What is the nature of the fat content of eating-chocolate, and what is the likely effect on serum cholesterol levels of the consumption of comparatively large amounts?*

A.—Eating-chocolate, whether plain or milk, contains between 30 and 35% fat. Cocoa butter is used in the manufacture because chocolate must be solid at room temperature but melt quickly at body temperature. Cocoa butter contains mainly relatively saturated fatty acids (iodine value about 37)—palmitic, stearic, and oleic—and only 2% of the essential fatty acid linoleic acid. The likely effect on serum cholesterol levels of consumption of comparatively large amounts is a rise from normal values.

Corrections.—There was a mistake in Table II in the article entitled "Action of Chlorothiazide and 'Oradon,' Alone and in Combination" by Drs. W. J. Poznanski and B. W. Cromie (June 20, p. 1553). The figure for total urinary mercury recovered should have been 849.98 mg. (not 1849.98 mg.).

Professor J. H. HALE has asked us to express his deep regret that the name of Dr. L. H. Lee was omitted inadvertently from the list of authors of the article entitled "Large-scale Use of Sabin Type 2 Attenuated Poliovirus Vaccine in Singapore During a Type 1 Poliomyelitis Epidemic" published in the *Journal* of June 20 (p. 1541).

The dosage of chlorpromazine reported in the article by Drs. J. R. Lawrence and M. J. W. Sando (*Journal*, August 1, p. 113) as being described by Laurence *et al.* (1958) should be 500 mg. intravenously, and not 50 mg. as printed on page 117.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Emergencies in General Practice (26s. 9d.).

Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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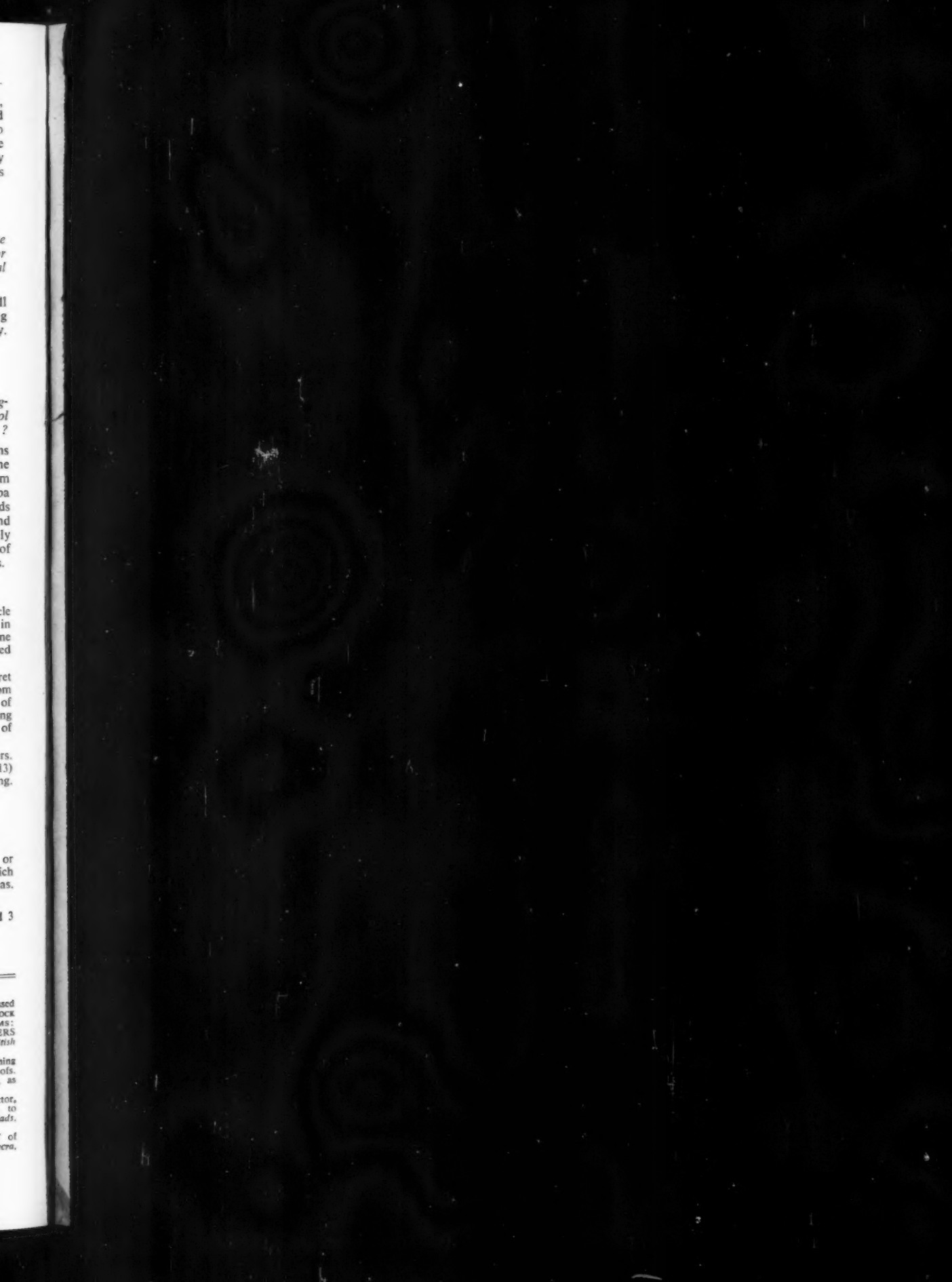
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